

allergywatch®

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



A PUBLICATION OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY

Volume 28, Number 5 • September-October 2026

Head and Neck

Klimek L, Mullol J, Ellis AK, et al. Current management of allergic rhinitis.

J Allergy Clin Immunol Pract. 2024;12(6):1399-1412.

Nearly 20% to 30% of adults and up to 40% of children experience allergic rhinitis (AR). Incidence peaks at age 20 to 40 years. Typical symptoms include rhinorrhea, nasal congestion, and itching; loss of smell is an indicator of severity. Seasonal AR is triggered by pollen. Perennial AR is triggered by house dust mite allergen, animal dander, and mold spores. Intermittent AR is defined as lasting less than 4 days per week or less than 4 consecutive weeks per year. Persistent AR lasts 4 or more days per week or 4 or more consecutive weeks per year.

Testing to differentiate AR from nonallergic rhinitis and local AR includes skin-prick testing (SPT) and serum allergen-specific IgE (sIgE) testing. Although not widely used, the best

test for differentiating local AR from nonallergic rhinitis is the nasal provocation test.

Treatment options include allergen avoidance, medication, and allergen immunotherapy. Medications include intranasal corticosteroids, intranasal antihistamines, oral antihistamines, leukotriene antagonists, intranasal and oral vasoconstrictors, and nasal rinses. Intranasal corticosteroids are the first-line therapy. Risks for systemic adverse events are lowest with mometasone furoate, fluticasone furoate, and fluticasone propionate because of their lower systemic absorption rates. In patients with moderate to severe AR, combinations of fluticasone propionate with azelastine and of mometasone furoate with olopatadine are effective. Biologics like omalizumab and dupilumab are not a first-line treatment.

Nonpharmacologic treatments include acupuncture, indoor air purifiers, masking, and nasal saline rinses. The probiotic bacteria *Lactobacillus rhamnosus* GG may prevent birch pollen-induced allergic asthma when administered intranasally. Ectoine nasal sprays contain a natural bacterial compound and may be an option for patients who wish to avoid the adverse effects of pharmacologic treatments.

COMMENT: Intranasal corticosteroids remain first-line across all severities and outperform oral antihistamines in real-world data. Systemic bioavailability differs widely, from under 0.6% for mometasone furoate, fluticasone furoate, and fluticasone propionate to above 46% for triamcinolone, flunisolide, and dexamethasone, which is worth considering to minimize the risk of systemic adverse effects. In pregnancy, loratadine and cetirizine have the strongest safety records; immunotherapy can be maintained but should not be initiated. The distinction between AR, nonallergic rhinitis, and local AR rests on where the IgE response occurs: local AR shows negative SPT and serum sIgE testing with positive nasal provocation testing, whereas nonallergic rhinitis is negative on all 3.

K.A.

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2026 Editor-in-Chief Disclosure:

Shyam R Joshi, 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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Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. J Allergy Clin Immunol. 2023;151(2):386-398.

This practice parameter provides GRADE-based guidance on managing chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults, covering intranasal corticosteroids (INCS), biologics, and aspirin therapy after desensitization (ATAD). Table 1 summarizes the panel's recommendations, and Table 3 the conditions important in shared decision-making.

Recommendation 1: In patients with CRSwNP, INCS rather than no INCS (conditional; low certainty of evidence). The delivery methods with most benefit are stent, spray, and exhalation delivery systems. Patient decision-making can be affected by cost, availability, accessibility, and practical implications of the different delivery methods.

Recommendation 2: In patients with CRSwNP, biologics rather than no biologics (conditional; moderate certainty of evidence). Biologics may be preferred in patients with greater disease severity and in those whose symptoms continue despite INCS for at least 4 weeks. In patients with aspirin-exacerbated respiratory disease (AERD), biologics may be preferred over ATAD in patients with a higher risk for harm with daily aspirin therapy.

Recommendation 3: In patients with AERD, ATAD rather than no ATAD (conditional; moderate certainty of evidence). Factors that increase bleeding risk affect the safety of long-term aspirin use. These include age, male sex, low body weight or body mass index, hypertension, diabetes, smoking, prednisone use, and history of gastrointestinal or intracranial bleeding.

Decision aids may be useful in helping patients arrive at a management decision. Development of the guidelines was supported by the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, & Immunology.

COMMENT: The practice parameter reports that INCS benefit varies by delivery method and outcome (rinse, spray, stent, and exhalation delivery each led on different clinical outcomes), with adverse effects no different from placebo. Among biologics, dupilumab was most beneficial across every outcome, with omalizumab and mepolizumab trailing depending on the end point, and a comorbidity treated by a given biologic reasonably drives that choice. ATAD applies only to patients with AERD and improves symptoms and quality of life but not smell, at the cost of bleeding and gastrointestinal effects that lead 1 in 10 patients to stop therapy. Surgery for CRSwNP was not assessed. K.A. ●

Savage TJ, Kronman MP, Sreedhara SK, et al. Treatment failure and adverse events after amoxicillin-clavulanate vs amoxicillin for pediatric acute sinusitis. JAMA. 2023;330(11):1064-1073.

Savage et al report that amoxicillin-clavulanate results in a slightly higher risk for treatment failure and a higher risk for gastrointestinal symptoms and yeast infections vs amoxicillin alone for treatment of acute sinusitis in children. Amoxicillin-clavulanate and amoxicillin are prescribed in up to 65% of cases of pediatric acute sinusitis. Clavulanate adds inhibition of bacterial β -lactamases. ● ● ●

The cohort study covered January 1, 2017, through December 31, 2021. Patients were identified by a diagnostic code for acute sinusitis and same-day prescription of antibiotics. The primary outcome was treatment failure, which was defined as a new antibiotic prescription, an emergency department or inpatient visit for acute sinusitis, or an inpatient visit for a related complication.

The propensity score–matched cohort included 99,471 children who received amoxicillin-clavulanate and 99,471 who received amoxicillin. Treatment failure occurred in 3.2% of children treated with amoxicillin-clavulanate and 2.9% of those treated with amoxicillin (relative risk [RR], 1.10; 95% CI, 1.05-1.16). Cephalosporins were the most frequently dispensed new antibiotic. Overall adverse events were more common in the amoxicillin-clavulanate group (2.3% vs 2.0%; RR, 1.15; 95% CI, 1.08-1.22). The risk for gastrointestinal symptoms (RR, 1.15) and yeast infections (RR, 1.33) was higher in the amoxicillin-clavulanate group. The authors reported some differences in the risk for treatment failure according to age. Study limitations included that all the children had commercial insurance, and data on race, ethnicity, and socioeconomic status were not available.

COMMENT: In this propensity-matched cohort, treatment failure was rare in both groups (3.1% overall) and serious failure very rare (0.05%). In the age-stratified analysis, the excess failure and adverse events with amoxicillin-clavulanate were limited to children aged 11 years and younger, with no difference in adolescents aged 12 to 17. The most common failure was a new antibiotic dispensed without a visit, which the authors suggest may reflect intolerance in younger children. The absolute effect was small, with an additional 357 children needing amoxicillin to prevent one failure.

K.A.

Seys SF, Schneider S, de Kinderen J, et al. Real-world effectiveness of dupilumab in a European cohort of chronic rhinosinusitis with nasal polyps (CHRINOSOR). *J Allergy Clin Immunol.* 2025;155(2):451-460.

This retrospective study analyzed real-world data for 752 patients with chronic rhinosinusitis with nasal polyps (CRSwNP) treated with dupilumab at 6 tertiary care centers in Europe. The study period covered December 2019 through September 2023. Data were collected from electronic medical records. Eligible patients had been treated with 300 mg dupilumab subcutaneously every 2 weeks for 24 to 52 weeks. Treatment response was assessed according to the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) 2021 criteria.

The patients' mean age was 50 years, and about 40% were female. Their mean BMI (in kg/m²) was 26.5. At baseline, their median Sinonasal Outcome Test 22 (SNOT-22) score was 52 and their median blood eosinophil count was 400 cells/ μ L. At 24 weeks, the patients' median SNOT-22

score had improved to 19; at 52 weeks it improved further to 16. At 52 weeks, 83% of patients experienced an improvement in SNOT-22 score of at least 8.9 points (the minimal clinically significant value). Dupilumab treatment also improved nasal polyp scores, total sinus symptoms, loss of smell, nasal blockage, and asthma control. Improvements in SNOT-22 score and nasal polyp score remained significant in subgroups of patients with asthma, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (NERD), and allergy.

The study was funded in part by Sanofi & Regeneron.

COMMENT: Every outcome in CRSwNP patients treated with dupilumab improved at 24 and 52 weeks, including nasal polyp score, SNOT-22 score, sinus symptoms, smell, and asthma control in those with comorbid asthma. Response was independent of age, sex, body mass index, smoking status, number of prior sinus surgeries, comorbid asthma, NERD, and baseline eosinophil count. A small cohort had previously received other biologics; the 22 patients switched from omalizumab showed similar trends, although the number was too small for statistical analysis. By 52 weeks, 68.2% of the entire cohort met the stringent EUFOREA 2021 response criteria.

K.A.

Dermatologic

Brooks SG, King J, Smith JA, et al. Cough and itch: common mechanisms of irritation in the throat and skin. *J Allergy Clin Immunol.* 2025;155(1):36-52.

Although cough and itch protect against foreign bodies and irritants, chronic cough and chronic pruritus can seriously impair quality of life. People with chronic cough (>8 weeks) have increased health care costs and higher rates of depression and anxiety. Chronic itch (>6 weeks) disrupts work and activities and leads to heightened anxiety and depression. Both conditions are more common in women.

Although patients with refractory chronic cough have increased histamine levels in their airways, histamine is not thought to play a major role in the condition. The P2X ion channels are a key mediator of refractory common cough. Sensory neurons like P2RX2 and P2RX3 are activated by extracellular ATP. The P2X3 antagonist gefapixant has shown efficacy in reducing awake-cough frequency in phase 3 clinical trials.

Most cases of chronic itch are mediated by nonhistaminergic pathways, but the histamine-mediated pathway plays a role in chronic urticaria. Second-generation H1-antihistamines (eg, loratadine, cetirizine) are first-line treatments for chronic spontaneous urticaria.

C-fibers and some A δ -fibers in the airway and skin have transient receptor potential (TRP) ion channels, including TRPA1, TRPM8, and TRPV4. In cough, TRPA1 is activated

by cigarette smoke and diesel fumes; TRPM8 is activated by cold and menthol. Therapies targeted against TRPs have shown mixed results. TRPV4 is associated with allergic contact dermatitis and chronic idiopathic pruritus.

Proinflammatory cytokines involved in itch include IL-4, IL-13, IL-31, IL-33, and TSLP. Medications targeting these cytokines have been shown to be effective in treating atopic dermatitis (ie, dupilumab, which targets IL-13 and IL-4).

Brain regions involved in the central mechanisms of cough and itch include the primary somatosensory cortex, which is the main activation center for the urge to cough, and the anterior cingulate cortex, which plays a role in the urge to scratch. The roles of brain regions in itch and cough are summarized in Table 1.

Nonpharmacologic treatments include speech and language therapy for refractory chronic cough and cognitive behavioral therapy for chronic pruritus.

COMMENT: In this extensive review article, the shared pathways of cough and itch are beautifully presented in Figure 2. TRP ion channels, particularly TRPV1, the capsaicin receptor, play a critical role in "itch transmission" in the skin and in the response to airborne irritants in the airway. Other pathways are also presented.

S.M.F.

Chinchilli E, De Benedetto A, Beck L. How we treat severe atopic dermatitis.

Ann Allergy Asthma Immunol. 2025;134:660-663.

Chinchilli et al describe their approach to treating atopic dermatitis (AD):

- Confirm diagnosis. The authors use the UK Working Party's diagnostic criteria. Diseases mimicking AD include graft-vs-host disease and paraneoplastic syndrome in adults and nutritional deficiencies and inborn errors of metabolism in children.
- Consider comorbidities. Nonatopic conditions include sleep disorders, viral and bacterial skin infections, and autoimmune disorders.
- Recommend topical treatments. Clinicians can educate patients about avoiding triggers and following good skin care practices. The authors advise their patients to moisturize the skin daily with nonprescription, fragrance-free creams or ointments.
- Prescribe topical corticosteroids or calcineurin antagonists. The authors have been successful in treating mild-to-moderate AD with ruxolitinib, which should be used on less than or equal to 20% of body surface area for up to 8 weeks. In patients whose symptoms do not improve after 4 weeks, the authors consider systemic treatments.
- Consider systemic treatments. As ranked by scores on the Eczema Area and Severity Index, the Itch Numerical Rating Scale, and the Dermatology Life Quality Index, the most effective FDA-approved treatments are as follows: high-dose (30 mg) upadacitinib > dupilumab = low-dose (15 mg)

upadacitinib = high-dose (200 mg) abrocitinib = lebrikizumab > tralokinumab = low-dose (100 mg) abrocitinib > nemolizumab. These authors recommend dupilumab as the first-line treatment. They prescribe JAK inhibitors primarily in younger, nonsmoking patients without obesity or a family history of deep vein thrombosis or pulmonary embolism, cancer, or cardiovascular disease. The authors may prescribe cyclosporine off-label (3-5 mg/kg/d) in patients for whom an injectable medication is not ideal (discontinuing within 1 year) or when added as a low dose (2-3 mg/kg/d) for a dupilumab-treated patient who has not met their treatment goal (tapering after 4-6 weeks).

COMMENT: The authors present their recommendations for treatment of AD using the 2023 updated practice parameters. Their flowchart (Figure 1) begins with an accurate diagnosis. Prior to biologics, topical treatment is recommended. Dupilumab is recommended for first-line systemic treatment. Interestingly, the authors recommend adding cyclosporine in selected patients before newer biologics or JAK inhibitors.

S.M.F.

Metz M, Giménez-Arnau A, Hide M, et al. Remibrutinib in chronic spontaneous urticaria.

N Engl J Med. 2025;392(10):984-994.

The phase 3 REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157) trials funded by Novartis Pharmaceuticals showed that oral remibrutinib 25 mg twice daily significantly improves itching and hives at 12 weeks in patients with symptomatic chronic spontaneous urticaria.

Patients eligible for trial enrollment were symptomatic despite treatment with a second-generation H1-antihistamine. They continued their use of H1-antihistamines during the trial. Patients were assigned 2:1 to oral remibrutinib or placebo for an initial treatment period of 24 weeks, followed by an open-label treatment period of 28 weeks during which all patients received the study drug. Patient-reported outcomes included itch severity, number of hives, angioedema activity score, and sleep and activity interference score.

In REMIX-1, 313 patients received remibrutinib and 157 received placebo; in REMIX-2, 300 patients received remibrutinib and 155 received placebo. At 12 weeks, the change from baseline in the weekly urticaria activity score was -20.0 in the treatment group vs -13.8 in the placebo group in REMIX-1 and -19.4 in the treatment group vs -11.7 in the placebo group in REMIX-2. Improvement was significantly greater in the remibrutinib groups in both trials. Patients experienced improvement as early as 1 week, and the improvements were sustained for 24 weeks. The percentage of patients with well-controlled chronic spontaneous urticaria at 2 weeks was significantly higher in the remibrutinib groups in both trials. About 31% of remibrutinib-treated patients in REMIX-1 and 28% of patients in REMIX-2 reported a complete absence of itch and hives at 12 weeks. The percentage of patients with at least one adverse

event was similar between groups. Most adverse events were mild or moderate. About 3% of remibrutinib-treated patients and 2% of placebo-treated patients reported at least one serious adverse event.

COMMENT: This paper reports the results of the pivotal clinical trials, REMIX 1 & 2, for efficacy of remibrutinib, an oral BTK inhibitor for adults with chronic idiopathic urticaria. Interestingly, remibrutinib had a rapid onset of action with noticeable improvement as early as the first week. Half of patients receiving remibrutinib improved by week 24 and one-third had complete absence of itch.

S.M.F.

Silverberg JI, Eichenfield LF, Hebert AA, et al. Tapinarof cream 1% once daily: significant efficacy in the treatment of moderate to severe atopic dermatitis in adults and children down to 2 years of age in the pivotal phase 3 ADORING trials.

J Am Acad Dermatol. 2024;91(3):457-465.

Tapinarof cream 1% is a topical steroid-free aryl hydrocarbon receptor agonist. The phase 3 ADORING trials studied the efficacy and safety of tapinarof for treatment of atopic dermatitis (AD) in patients aged 2 years and up.

In the randomized double-blind trials, eligible patients were assigned 2:1 to tapinarof cream or a vehicle cream. Most patients had moderate disease at baseline, as defined by a Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of at least 3. The primary end point was the proportion of patients achieving a vIGA-AD score of 0 (clear) or 1 (almost clear). A secondary end point was the proportion of patients with at least 75% improvement in Eczema Area and Severity Index (EASI) score at 8 weeks (EASI75). About 400 patients were randomly assigned to study groups in each trial. Most (80%) were younger than 18 years of age.

Significantly more patients treated with tapinarof cream than with the control achieved a vIGA-AD score of 0 or 1: 45.4% vs 13.9% in ADORING 1 and 46.4% vs 18.0% in ADORING 2. An EASI75 response was achieved in 55.8% of tapinarof-treated vs 22.9% of control-treated patients in ADORING 1 and in 59.1% vs 21.2% of patients, respectively, in ADORING 2. Tapinarof also significantly improved itch and Peak Pruritus Numerical Rating Scale responses. Treatment-emergent adverse events included folliculitis, headache, and nasopharyngitis.

The trials were sponsored by Dermavant Sciences, Inc.

COMMENT: This paper presents the results of the pivotal clinical trial using topical tapinarof 1%, a nonsteroidal cream, in a diverse population of patients with AD down to 2 years of age. Since tapinarof's mechanism of action is an aryl hydrocarbon receptor agonist, the adverse event profile is more favorable, particularly in young children. The primary end point assessment of improvement was an impressive 31.5% in ADORING 1 and 28.5% in ADORING 2.

S.M.F.

Lung

Castro-Rodriguez JA, Wolters AAB, Rodriguez-Martinez CE, et al. Risk factors and mechanisms leading to preschool recurrent wheeze and asthma.

J Allergy Clin Immunol Pract. 2025;13(10):2537-2551.

Biological and familial risk factors for recurrent preschool wheezing include male sex and having a first-degree relative with a history of atopy, asthma, allergic rhinitis, and/or wheezing. Environmental factors include exposure to tobacco smoke and use of gas as a fuel for cooking. Children born by cesarean delivery, prematurely, in warmer climates, or during the second half of the year are at greater risk for developing recurrent wheeze. Associations with prenatal vitamin D levels or with the consumption of ultra-processed foods are inconsistent. Infants with severe respiratory tract infections, such as with respiratory syncytial virus (RSV) or rhinovirus, appear to be at higher risk of developing asthma.

The genetic locus most consistently associated with recurrent wheeze and childhood asthma is 17q12-21, or 17q. Epigenetic changes like DNA methylation are associated with childhood-onset asthma (the article's Table 2 lists CpG sites associated with recurrent preschool wheeze).

Biomarkers that can be assessed noninvasively, such as allergen sensitization, blood eosinophil levels, fractional exhaled nitric oxide (FeNO), and volatile organic compounds in exhaled breath, may help to guide treatment decisions. However, accurate measurement of FeNO and volatile organic compounds can be challenging in young children. Because most preschool children with asthma have normal lung function, early assessment of lung function cannot confirm or exclude an asthma diagnosis.

COMMENT: Susceptibility to recurrent preschool wheeze and asthma consists of a complex interaction between host susceptibility and environment. These authors identify 6 domains of risk factors: (1) biological, genetic, and familial; (2) behavioral and social; (3) environmental and socioeconomic; (4) medical conditions; (5) early life exposures; and (6) parental and prenatal stress exposure. The strongest risk factor for asthma is a first-degree relative with asthma, and the strongest associated gene locus is 17q (eg, *ORMDL3* and *GSMD3*). Epigenetic changes associated with environmental exposures (smoking or pollution exposure) can lead to DNA methylation changes that are also strongly associated. Sensitization to allergens is a key risk factor for development of preschool asthma and recurrent wheeze, whereas other biomarkers typically predict phenotype or endotype.

C.A.S.

LaForce C, Albers F, Danilewicz A, et al. As-needed albuterol-budesonide in mild asthma.
N Engl J Med. 2025;393(2):113-124.

People with mild asthma can experience severe exacerbations. These data from the phase 3b multicenter BATURA trial (NCT05505734) provided evidence for as-needed albuterol-budesonide in patients with uncontrolled mild asthma. Eligible participants had uncontrolled asthma despite treatment with a short-acting β_2 -agonist (SABA) with or without a low-dose inhaled glucocorticoid or leukotriene-receptor antagonist. They were assigned in a double-blind manner to albuterol (180 μ g) plus budesonide (160 μ g) or albuterol alone (180 μ g) as needed for 52 weeks. The combination treatment was delivered in a single pressurized, metered-dose inhaler. The primary end point was the first severe asthma exacerbation. Secondary end points included annualized rate of severe asthma exacerbations and annualized total exposure to systemic glucocorticoids.

2516 participants were randomly assigned, of whom 71% completed the trial. The most common reason for withdrawal was loss to follow-up. Most participants were adults; 68% were female and 70% were White. Only 11% had experienced a severe exacerbation in the year before the trial.

The percentage of participants with a first severe exacerbation was significantly lower in the albuterol-budesonide treatment group than in the albuterol-alone group. The annualized rate of severe exacerbations was 0.15 in the combined group vs 0.32 in the albuterol-alone group. Exposure to systemic glucocorticoids was lower in the albuterol-budesonide group. The rate of adverse events was similar (about 42% in the albuterol-budesonide group and 43% in the albuterol group).

Because of the significantly lower risk for severe exacerbations with combined treatment, the trial was ended early at the planned interim analysis. The trial was funded by Bond Avillion 2 Development and AstraZeneca.

COMMENT: This phase 3b clinical trial in patients with mild asthma evaluated the question of as-needed albuterol-budesonide compared with albuterol alone. Randomization was well balanced, with around 1200 participants in each group. A severe exacerbation occurred in 5.1% of the participants in the albuterol-budesonide group and in 9.1% in the albuterol group (hazard ratio, 0.53). The annualized rate of severe asthma exacerbations was lower with albuterol-budesonide. The rate of local glucocorticoid-related adverse events was similar in the 2 groups: 1.6% in the albuterol-budesonide group vs 0.6% of the albuterol-alone group. Local glucocorticoid-related adverse events were reported more often by those who had only ever used albuterol at baseline.

C.A.S.

Murphy VE, Gibson PG, Schatz M. Managing asthma during pregnancy and the postpartum period.
J Allergy Clin Immunol Pract. 2023;11(12):3585-3594.

Asthma worsens during pregnancy in about 40% of women, and about 20% of women will experience exacerbations needing treatment. Exacerbations are most common in the second trimester. Black women have an increased risk for exacerbations (relative risk [RR], 1.62; 95% CI, 1.52-1.73). Other patients with increased risk are those who are multiparous, who have obesity, who were experiencing exacerbations before pregnancy, and who have poor asthma control.

Asthma during pregnancy increases the risk for maternal complications including gestational diabetes (GDM) and preeclampsia and poor birth outcomes like low birth weight and preterm birth. In one large cohort study, 15% of pregnant women with asthma had GDM. The risk for low birth weight is increased 46% in women with asthma, with a mean reduction in birth weight of 93 g.

Because the risk for exacerbations outweighs the medication risks, asthma medications are “broadly considered safe” during pregnancy. Albuterol is the best-studied short-acting β -agonist (SABA). Budesonide or fluticasone are recommended inhaled corticosteroids (ICSs) for women starting an ICS during pregnancy. Long-acting β -agonists (LABAs) can be used in combination with an ICS. Omalizumab is the best-studied biologic.

Steps in medication management of asthma during pregnancy are presented in Table 5: (1) SABA as needed. (2) Low-dose ICS. (3) Low-dose ICS-LABA. (4) Medium-dose ICS-LABA. (5) Consider tiotropium, azithromycin, and biologics. (6) Oral corticosteroids at lowest effective dose.

More research is needed on single-inhaler maintenance and reliever therapy and fractional exhaled nitric oxide (FeNO)-guided asthma management. FeNO-guided asthma management can reduce exacerbations during pregnancy. Telehealth may have applications to optimize medication adherence, inhaler device technique, and asthma knowledge.

COMMENT: Exacerbations during pregnancy can in turn increase risks for low birth weight, preterm birth, cesarean delivery, small-for-gestational age infants, and increased risk of asthma in the baby’s early childhood. Good management of asthma during pregnancy, however, can offset the risks for negative outcomes. Continued use of well-tolerated ICS, LABAs, and SABAs to maintain control of asthma throughout pregnancy and breastfeeding is guideline-recommended with additional evidence of benefit to the neonate. Discussions with pregnant women should recognize that around 40% will become nonadherent to ICS without encouragement. No studies of as-needed ICS-LABA/SABA combos have been done specifically in pregnancy.

C.A.S.

Nguyen TH, Elios M, Fitzpatrick AM, et al. Optimizing pediatric asthma management: implementation and evaluation of anti-inflammatory reliever and single maintenance and reliever therapies.

J Allergy Clin Immunol Pract. 2025;13(7):1507-1515.

This review presents updated guidance on maintenance and reliever therapies for children. Newer asthma therapies include anti-inflammatory reliever (AIR) therapy for step 1 to 2 asthma management with an as-needed inhaled corticosteroid (ICS) plus a fast-acting bronchodilator. Single maintenance and reliever therapy (SMART) incorporates an ICS and a long-acting β_2 -agonist (LABA) in a single inhaler.

Accurately diagnosing asthma in children can be challenging because symptoms overlap with other respiratory conditions. Spirometry is recommended in children ages 5 and up. Impulse oscillometry can be used in younger children. Fractional exhaled nitric oxide assessment can be used for diagnosis and assessment, especially in children with allergic or eosinophilic asthma. Best practices for monitoring include regular follow-up.

Benefits of AIR therapy and SMART in children include reducing the risk for future exacerbations, reducing lung inflammation (compared with use of short-acting β_2 -agonist alone), providing better control of asthma symptoms, and potentially reducing cumulative steroid exposure. Barriers may exist to real-world application of guidelines. For example, most insurance plans cover only one canister per month, and clinician knowledge of current guidelines can vary. In one study, a majority of clinicians incorrectly chose ICS/salmeterol as an option for SMART, but the slow mechanism of action of salmeterol makes it inappropriate for use as a reliever therapy.

COMMENT: These authors note that for patients aged 12 years and older, GINA currently recommends considering as-needed low-dose ICS-formoterol as an AIR therapy for mild asthma and SMART for moderate-to-severe persistent asthma. They also note, however, that there is less evidence to support SMART in children aged less than 12 years, for which there is only one randomized clinical trial in children aged 4 to 11. Real-world barriers to AIR and SMART include a shortage of ICS-formoterol combinations and lack of FDA approval for these as AIR and SMART reliever indications. Thus, variable prescription drug formularies may affect access. Meanwhile, SMART regimens in those ages 12 and up appear to have greater cost-effectiveness in asthma control, in addition to greater treatment effectiveness leading to reduced use of oral corticosteroids for exacerbations.

C.A.S.

Food and Drug Allergy/Hypersensitivity Reactions

Bartha I, Almulhem N, Santos AF. Feast for thought: a comprehensive review of food allergy 2021-2023.

J Allergy Clin Immunol. 2024;153(3):576-594.

As highlighted by Bartha et al, hospital admissions for food allergy (FA)-caused anaphylaxis have increased; most deaths are due to cow's milk or nut allergy. Egg allergy is more likely to be outgrown than peanut allergy; new onset of egg allergy is rare after 1 year of age. Animal models show that damage to the gut epithelial barrier may play a role in the development of FA. Biomarkers of peanut allergy include peanut-specific IgE levels, the ratio of peanut-specific IgE to total IgE, the ratio of peanut-specific IgE to IgG4, and a higher frequency of peanut-specific effector T cells.

Newer in vitro diagnostic tests include the basophil activation test (BAT) and the mast cell activation test (MAT). In the BAT2 study, the BAT showed 100% accuracy in diagnosing egg allergy. The MAT has similar specificity but lower sensitivity in diagnosing peanut allergy.

Table 2 summarizes experimental findings, such as the following:

- Baked milk oral immunotherapy (OIT) improves quality of life with a good safety profile in children aged 3 to 18 years.
- Epicutaneous immunotherapy (eg, peanut patch VP250) is safe and well tolerated in children with peanut allergy.
- Peanut sublingual immunotherapy was shown to induce desensitization in 70% of children aged 1 to 11 years.
- As an adjunct to OIT, omalizumab increases the dose of food tolerated, reduces allergic reactions, and improves quality of life.

COMMENT: This update names new risk factors, such as *HLA-DQA1*01:02*, a human leukocyte antigen (HLA) polymorphism, for peanut allergy and cannabis exposure for non-specific lipid transfer protein allergy. Figure 2 summarizes novel immune mechanisms:

- Gut epithelial damage from detergents and rinse aids may increase FA risk.
- Filaggrin loss of function is associated with persistent FA.
- Ara h 1, 2, and 3 are cross-reactive.
- FA reaction severity is associated with α -tryptase and basophil activation.

Table 1 lists suggested skin-prick and IgE cutoffs for different types of FA. The review suggests that adding epitope assays or BAT can further improve specificity. Immunotherapy approaches for FA may be more effective in younger patients. Finally, early allergen introduction benefits all risk subgroups, but emollient interventions in infancy do not appear to prevent eczema according to a Cochrane review.

G.B.L.

Gupta E, Conway AE, Verdi M, et al. Food allergy, nutrition, psychology, and health.
J Allergy Clin Immunol Pract. 2025;13(4):773-782.

The article explores the intersection of nutrition and psychology. People with food allergy (FA) have less “food freedom,” described here as “freedom to consume and enjoy different foods, as well as the freedom associated with not needing to engage in the cognitive, emotional, social, and financial burdens that come with managing a chronic food allergy or hypersensitivity.” Anxiety around eating can lead to avoidant/restrictive food intake disorder (ARFID), which is distinct from other eating disorders like anorexia nervosa and bulimia nervosa because patients do not have altered body image or weight concerns. Taste aversion, particularly in children older than 6 years, can be a barrier to adherence with oral immunotherapy. Studies have reported that children with FA have a distinct salivary microbiome and fewer fungiform papillae on the tongue.

Strategies to minimize feeding issues, as summarized in Table 2, include introducing foods between 4 and 6 months of age when the infant appears to be developmentally ready; offering a variety of foods from each food group; establishing family meal routines in which children and their caregivers eat together; and serving meals and snacks at the table.

Psychological interventions to improve the quality of life of families with FA include cognitive behavioral therapy, acceptance and commitment therapy, mindfulness-based stress reduction and body scanning, biofeedback, support groups, and empowerment through shared decision-making. **COMMENT:** A surprising 9% of children with FA are reported to have experienced stunted growth, and 13.6% to 40% may have feeding difficulties. Elimination diets may increase the risk of ARFID, which may be seen in up to 37% of children with FA. Elimination diets may also affect the gut microbiome, which may impact behavior and cognition through the “gut-brain axis.” Table 3 lists features of a gut-friendly diet, including avoiding processed foods and consuming fruits and vegetables. Table 4 lists psychological interventions to address FA anxiety and states that the most effective educational intervention is shared decision-making, which empowers patients to attain control over their FA. G.B.L. ●

Kroshinsky D, Cardones ARG, Blumenthal KG. Drug reaction with eosinophilia and systemic symptoms.
N Engl J Med. 2024;391(23):2242-2254.

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, T cell-mediated skin reaction to prolonged medication exposure. In the prodromal phase, patients experience fever, malaise, sore throat, dysphagia, pruritus, and a burning skin sensation. This is followed by a rash starting on the trunk and face that can spread to more

than 50% of the body. Patients may have follicular pustules on their face, neck, and chest. Systemic symptoms include lymphadenopathy, hematologic changes, hepatitis, and acute kidney injury. Some 10% of patients may experience persistent complications years after the initial episode.

The differential diagnosis includes Stevens–Johnson syndrome, hemophagocytic lymphohistiocytosis, and acute graft-versus-host disease. Stevens–Johnson syndrome resolves more rapidly within 3 to 4 weeks. DRESS is a Th2-predominant inflammatory reaction. Some evidence suggests that DRESS is distinguished by an imbalance in the number of regulatory T cells. Patients with kidney impairment have an increased risk for allopurinol-related DRESS. Lung involvement manifests as shortness of breath, dry cough, or both, and pulmonary DRESS is often misdiagnosed as pneumonia. Myocarditis can appear after a delay of months.

The first step in treatment is to identify and discontinue the suspected causative drug. No validated test for establishing drug causality exists. Once patients are no longer being treated with systemic glucocorticoids, delayed intradermal tests and patch testing may be used to identify the causative drug. Drug challenge with a potential culprit drug is contraindicated in almost all cases. Allergists and immunologists can help in assessing causative drugs and choosing alternatives.

COMMENT: Allopurinol, vancomycin, lamotrigine, carbamazepine, and trimethoprim-sulfamethoxazole account for most US cases of DRESS. Most cases occur after 2 to 6 weeks of continuous drug exposure. Facial edema distinguishes DRESS from other morbilliform drug rashes. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system is used for diagnosis; scores higher than 5 indicate definite disease. Recent guidelines recommend testing patients for reactivation of HHV-6. Glucocorticoids are the mainstay of treatment, with a 6- to 12-week gradual taper to reduce relapse risk. Anti-IL-5 therapies may be a more accessible and safer therapy for induction, and azathioprine and mycophenolate are steroid-sparing options for maintenance therapy. After resolution, testing for DRESS culprits includes delayed intradermal testing, patch testing, HLA testing, ELISpot, and lymphocyte transformation testing. G.B.L. ●

Wang C, Ramsey A, Lang D, et al. Management and prevention of hypersensitivity reactions to radiocontrast media: a consensus statement from the American College of Radiology and the American Academy of Allergy, Asthma, & Immunology.
J Allergy Clin Immunol Pract. 2025;S2213-2198(25)00191-6.

This multidisciplinary task force developed consensus recommendations for use of contrast media and management of contrast-associated reactions. Most anaphylactic reactions to iodinated contrast media (ICM) occur within 15 to 30 minutes; patients should be monitored accordingly. ● ● ●

Vasovagal reactions include pallor, weakness, nausea, vomiting, diaphoresis, bradycardia, and hypotension but not the urticaria, angioedema, flushing, and pruritus seen in anaphylaxis. The 2 most important steps in managing an anaphylactic reaction are to (1) stop the ICM infusion and (2) administer epinephrine (0.01 mg/kg intramuscular of a 1-mg/mL concentration). Glucocorticoids are not recommended for treatment of acute anaphylaxis nor for preventing biphasic anaphylaxis.

Key takeaways include:

- Clinicians should document any ICM hypersensitivity reactions in the patient's electronic medical record, including symptoms and specific causative agent.
- For patients with a history of *mild* immediate hypersensitivity reactions, premedication is not recommended. Switching the contrast agent is recommended when feasible.
- For patients with a history of *moderate* immediate hypersensitivity reactions, switching the contrast agent is recommended when feasible. Premedication may be considered.
- For patients with a history of *severe* immediate hypersensitivity reactions, the task force recommends first considering alternative imaging studies. If no alternative imaging study is an option, premedication is recommended, and switching the contrast agent is recommended when feasible.

COMMENT: Despite its prevalent use, there is no high-quality evidence that corticosteroid premedication prevents recurrent immediate reactions to low-osmolality contrast media. Instead, switching the ICM agent may be more effective than premedication, although for severe reactions, an alternative imaging modality should be considered. Skin-prick testing to full strength and intradermal testing to 1:10 diluted ICM can be performed to identify a tolerated ICM agent. Delayed reactions such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens–Johnson syndrome have also been reported. There is no clear evidence that seafood, iodine, or gadolinium allergy are risk factors for ICM reactions.

G.B.L.

Anaphylaxis

Almaci M, Treudler R, Breiding M, et al. Allergen immunotherapy-induced anaphylaxis: data from the European Anaphylaxis Registry. *Ann Allergy Asthma Immunol.* 2025;134(6):724-730.

Using data from 54 allergy centers in the European Anaphylaxis Registry, the study reports the incidence of anaphylaxis resulting from allergen immunotherapy (AIT). Of 15,748 reported cases of anaphylaxis, 1.1% were caused by AIT.

Of the 173 cases of AIT-induced anaphylaxis, 88% were caused by subcutaneous immunotherapy (SCIT) and about

5% by sublingual immunotherapy (SLIT); the route of administration was unknown for 12 cases. Most reactions were grade 2, and most occurred within 30 minutes of allergen application. Among the patients who experienced AIT-induced anaphylaxis, more children than adults had asthma (49% vs 23%, respectively). Among cases of AIT-induced anaphylaxis with known allergen extracts, 51% were caused by pollen allergen extracts; about 30% were caused by insect venom and 19% by house dust mite allergen extract. In both age groups, corticosteroids and antihistamines were the most frequently administered first-line treatment. Adrenaline was used less often in adults than in children and adolescents.

In this European registry, grade 3 reactions were reported more frequently in children and adolescents than in adults. Adrenaline was underused as a first-line treatment of anaphylaxis.

COMMENT: This study analyzed 173 cases of AIT-induced anaphylaxis from registry data (2007–2023), representing 1.1% of all anaphylaxis cases. Pediatric cases accounted for 1.8% of all anaphylaxis cases; adults for 0.7%. Respiratory symptoms were more frequent in children and adolescents (92%) than in adults (66%). Grade 3 reactions were more frequent in children and adolescents (39%) than in adults (27%). Most anaphylaxis cases were associated with SCIT (n=153). Pollen extracts were the most common cause of AIT-induced anaphylaxis, followed by insect venom and house dust mite. One fatality was reported due to grass pollen SCIT. Epinephrine was administered in only 30% of grade 2 and 50% of grade 3 reactions.

S.W.S.

Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus placebo in indolent systemic mastocytosis. *NEJM Evid.* 2023;2(6):EVIDoA2200339.

Most patients with indolent systemic mastocytosis (ISM) have a D816V mutation in the *KIT* gene, resulting in autoactivation of the KIT receptor tyrosine kinase. Avapritinib is an oral, potent, selective inhibitor targeting the mutated tyrosine kinase. The PIONEER trial studied the efficacy and safety of 25 mg avapritinib once daily (NCT03731260).

Eligible patients were adults with uncontrolled, moderate-to-severe ISM symptoms despite best supportive care. The primary end point was mean change in total symptom score at week 24. The trial was sponsored by Blueprint Medicines Corporation.

Throughout 42 sites in 13 countries, 141 patients were assigned to avapritinib and 71 to placebo. Patients ranged in age from 18 to 79 years, and nearly three-quarters were women. The treatment group experienced a significantly greater decrease in mean symptom score vs the placebo group (–15.6 points vs –9.2 points). About 54% of the treatment group experienced a reduction in serum tryptase level of 50% or more. No patients in the placebo group

achieved this end point. More patients in the treatment group experienced a reduction in *KIT* D816V variant allele fraction in peripheral blood (68% vs 6% in the placebo group). One-quarter of patients in the treatment group experienced a reduction in total symptom score of 50% or greater (vs 10% in the placebo group). More patients receiving avapritinib than placebo had discontinued best supportive care treatments by week 24. Most adverse events ascribed to avapritinib were grade 1 or 2, including flushing, edema, increased alkaline phosphatase, and insomnia.

COMMENT: Avapritinib is the first and only approved targeted therapy for adults with ISM in the United States and the European Union. Approval was based on results from this phase 2 trial demonstrating superiority over placebo. From baseline to week 24, avapritinib-treated patients had a decrease in mean total symptom score of 15.6 points compared with 9.2 points in patients receiving placebo. Additionally, 76/141 patients (54%) receiving avapritinib achieved a greater than or equal to 50% reduction in serum tryptase level and 56/106 (53%) had a greater than or equal to 50% reduction in bone marrow mast cell burden. Adverse events resulting in treatment discontinuation were uncommon (2% vs 1%).

S.W.S.

Pernea P, Méni C, Rossignol J, et al. Characteristics and therapeutic strategies for diffuse cutaneous mastocytosis. *JAMA Dermatol.* 2025;161(8):855-862.

Diffuse cutaneous mastocytosis (DCM) is a rare mastocytosis in children in which mast cells infiltrate the entire skin. In this cohort of 33 children with DCM in France, about 54% were male and the mean age of disease onset was 2.2 months. Four children had aggressive systemic mastocytosis (ASM) that could not be distinguished clinically from DCM, and all of these children had *KIT* codon 816 variants.

The patients with ASM had a higher mean baseline tryptase concentration than the DCM group. Spontaneous regression of disease was analyzed in 15 children not treated systemically. Of these, 13 children experienced regression of their disease after a mean follow-up time of 12.9 years. Seven patients were treated with tyrosine kinase inhibitors or mammalian target of rapamycin inhibitors. In an analysis combining the current study cohort with data from case reports identified by literature review, the authors found that children without the *KIT* codon 816 variant were more likely to experience spontaneous regression.

The authors identify 2 main presenting features that should alert clinicians to DCM: “early, extensive bullous [mast cell] degranulation and skin infiltration with Darier-like urticaria.” Because of the more frequent occurrence of anaphylaxis in infants with DCM than in those with maculopapular cutaneous mastocytosis (MPCM), the authors recommend prescribing epinephrine autoinjectors for all patients with DCM.

COMMENT: DCM is distinguished by diffuse, dense infiltration of neoplastic mast cells throughout the dermis and is associated with mediator-related symptoms and risk of anaphylactic shock. Compared to MPCM, patients with a clinical presentation of DCM in this single-center cohort had a higher mean baseline serum tryptase level (47.5 vs 7.4 $\mu\text{g/L}$), a higher prevalence of anaphylaxis (4 [12.1%] vs 5 [2.4%]; $P = .02$), and a more frequent association with ASM. *KIT* codon 816 variants were identified in 4 patients; all of whom had ASM. Cyto-reductive treatment may benefit select high-risk cases of DCM.

S.W.S.

Stiles SL, Sanfilippo FM, Murray K, et al. Investigating health care pathways for anaphylaxis: seeing the bigger picture through linked data.

***J Allergy Clin Immunol Glob.* 2024;4(1):100371.**

These authors from Australia studied characteristics of patients with anaphylaxis according to where they first sought care. Using linked data sets, the authors analyzed all points of a patient’s health care interactions during a single anaphylaxis event.

The study identified 6 care pathways. About half of the anaphylaxis events resulted in hospital admission. Care was first provided in the ED in 59% of cases; most events were treated in the ED at some time during the care pathway. For about 64% of events, the trigger of the anaphylaxis was not identified. About half of the events were included in 2 different data sets (ambulance and ED, ED and hospital, or ambulance and hospital). The study identified discrepancies in coding. Of 19 anaphylaxis-coded deaths, only 5 were associated with an event in the data records. The authors also identified 9 additional deaths occurring within 2 days of an anaphylaxis event that were not coded as anaphylaxis deaths.

Over the 7-year period examined, the most common care pathways for anaphylaxis in Western Australia were initial care in the ED followed by hospital admission or ED care alone. Although Australian anaphylaxis guidelines recommend transport by ambulance to the ED, more people came directly to the ED. Older adults were more likely than those aged 25 to 34 to call an ambulance.

COMMENT: In this retrospective cross-sectional study of 16,456 anaphylaxis events (13,607 people), the most common pathway involved initial care in the ED followed by hospital admission (30.6%) or ED care alone (23.5%). Most events (59%) presented first to the ED, 36% to ambulance, and 5% to the hospital directly. Metropolitan residency and age greater than 65 years were most strongly associated with calling an ambulance. Food-triggered anaphylaxis was associated with hospital admission (odds ratio [OR], 1.52), especially if an ambulance was the first contact of care (OR, 5.14). Children, older adults, and those with comorbidities

were also more likely to be admitted. This study highlights discrepancies in how anaphylaxis is coded and recorded across ambulance, ED, and hospital data sets.
S.W.S.

Immune Hypersensitivity Disorders

Ahsan DM, Elieh-Ali-Komi D, Pereira MP, et al. Subtypes of atypical cold urticaria and recommendations for their diagnostic workup. J Allergy Clin Immunol Pract. 2025;13(9):2370-2380.

Ahsan et al present a diagnostic workup for *atypical* cold urticaria. These patients show atypical or negative results on standard cold stimulation tests like the ice cube test. Through a systematic literature review (through 2025), the authors identified 10 subtypes of atypical cold urticaria. Among these are a delayed form (with wheals appearing 15-20 minutes after cold exposure), a type with aberrant wheals, a type in which wheals were localized to specific areas of the body, a cholinergic form in which psychological stress enhanced wheal development, a water-dependent type, and a food-dependent type.

Figure 3 presents a diagnostic algorithm for diagnosing each of the 10 subtypes. For all patients with suspected cold urticaria, the first step is a standard cold stimulation test (eg, the ice cube test, TempTest [Courage + Khazaka electronic GmbH], or both). In patients with negative results on the standard test, a detailed medical history is taken to select an appropriate modified cold stimulation test. Patients should be asked about (1) the trigger of the cold-induced whealing, (2) the duration of exposure, (3) where the wheals occurred, and (4) potentially relevant factors like humidity or whether they were exercising.

As an example, in a woman who reported a delayed appearance of wheals, the authors used an ice cube test with an extended observation time of 15 minutes to confirm a diagnosis of the delayed subtype of cold urticaria. In a woman who reported a history of wheals and angioedema after exposure to cold air, the authors used a cold room test (18 degrees Celsius) combined with wind exposure from an air conditioner for 15 minutes to confirm a diagnosis of the generalized cold exposure subtype.

COMMENT: Diagnosing cold urticaria can be challenging because standardized approaches may miss some patients. The authors share valuable insights on a protocol for modified cold stimulation tests for 10 subtypes of atypical cold urticaria. This publication gives us improved tools for diagnosing patients with the goal of improving their medical care.
V.H.T.

Dominy J, Koch C, Arnold C, et al. Caspase 1-deficient humans survive into late adulthood despite dramatically lower canonical inflammasome activity. J Allergy Clin Immunol. 2026;157(1):217-225.

"CASP1-deficient individuals show no obvious pathology, are capable of having children, and report no history of recurrent infection," report the authors of this clinical profile of people homozygous for a loss-of-function *CASP1* variant. Caspase-1 (also called IL-1-converting enzyme) activates IL-1 β and IL-18, and increased CASP1 activity is associated with inflammatory conditions. Some patients with autoinflammatory disease have decreased activity. Using data from the Pakistan Genome Resource, the authors identified 8 individuals with *Tyr153*/Tyr153** variants of *CASP1* who produced no functional protein.

Individuals with the *Tyr153*/Tyr153** genotype ranged in age from 14 to 70 years and had undetectable serum CASP1 protein levels. In heterozygotes, CASP1 protein levels were 71% lower than in reference homozygotes. Loss or complete absence of CASP1 protein was associated with lower IL-18, IL-1 β , and IL-1 β -induced IL-6. In most participants lacking CASP1, IL-18 was undetectable. Loss of function was also associated with a reduction in white blood cells, notably neutrophils and monocytes. The authors hypothesize that the reduced neutrophil levels were the result of the lowered IL-1 β and IL-18.

Both men and women identified as loss-of-function homozygotes had children. Through multiple generations, CASP1 deficiency did not overtly increase the risk for infectious disease. The authors note that this observation is in contrast with findings in *Casp1* knockout mice, which show increased susceptibility to microbial challenge.

COMMENT: While rare, we may provide medical care for patients with homozygous loss-of-function variants in *CASP1*. The authors provide reassuring data that we can share with these patients. While decreases in IL-1 β , IL-18, and neutrophil counts were described, neither increased risk of infection nor negative effects on human reproduction were reported. This arms the practicing immunologist with updated information about a rare disease that we can share with our patients and their family members.
V.H.T.

Knight V, Sepiashvili L. Cytokine testing and challenges for diagnostic and clinical monitoring use. J Allergy Clin Immunol. 2025;155(2):410-413.

Cytokines, which include proinflammatory, anti-inflammatory, and regulatory cytokines, are secreted proteins that play roles in cell communication. Their levels are measured in the diagnosis, treatment, and monitoring of inflammatory diseases. For example, IL-1 β may be elevated during flares of autoinflammatory diseases. Because cytokines have

short half-lives, however, the timing of sample collection is important, and samples should be analyzed as soon as possible after collection. Because of significant variability among laboratory-developed cytokine assays, clinicians should use the same laboratory and the same assay platform for sequential measurements. Soluble cytokine receptors and cytokine-targeting biologics can interfere with measurement. For example, soluble cytokine receptors can form complexes with a target cytokine and block antibody binding, thus giving false-negative results on immunoassays that rely on antibody-based capture and detection.

Because of the limitations of cytokine measurement, surrogate markers may provide more accurate information. For example, CXCL-9, which is induced by interferon- γ , may be a more accurate measure of response to emapalumab. In patients treated with siltuximab, IL-6 may be measured before the initiation of therapy, but serum IL-6 measurement is not recommended during therapy because levels can be falsely elevated. Surrogate markers include C-reactive protein, ferritin, and CXCL13. CXCL13 correlates with treatment response in patients with idiopathic multicentric Castleman disease.

Table 1 lists disease states in which cytokine measurement may be useful and suggests surrogate markers for use in patients treated with anticytokine biologics.

COMMENT: The use of biomarkers is expanding, and our understanding of their utility is also improving. This manuscript is an excellent review of cytokines and their receptors. The authors provide a practical review of cytokines, the disease states in which measurements can be helpful, timing for measurement, and current biologic therapies. This can serve as a practical tool for our day-to-day approach in the allergy/immunology clinic.

V.H.T.

Zuzolo J, Zulfiqar MF, Spoelhof B, et al. Functional testing of humoral immunity in the Pevnar 20 era. *Ann Allergy Asthma Immunol.* 2025;134(3):279-283.

Insurers often require laboratory results showing an inadequate antibody response to vaccination before approving treatments like immunoglobulin replacement therapy. PPSV23 (the 23-valent pneumococcal polysaccharide vaccine) is the most common vaccine used for functional testing of humoral immunity. This article reports that, even in the era of pneumococcal conjugate vaccines (PCVs), PPSV23 is valuable for diagnosing humoral immune deficiencies, with an accuracy of 81% to 84%.

Clinical practice guidelines define an adequate antibody response to PPSV23 as a titer of greater than or equal to 1.3 $\mu\text{g/mL}$ in addition to a 2- to 4-fold increase in titer over baseline. These guidelines remain controversial because of challenges in interpreting vaccine responses. For example, people with higher antibody titers at baseline are less likely to experience a 2-fold increase.

In contrast with PPSV23, which triggers a T cell-independent antibody response, PCVs trigger a T cell-dependent antibody response. In patients who have received a PCV, a pure B-cell response to PPSV23 can be assessed only by evaluating the PPSV23 serotypes not included in the previously administered PCVs. To aid clinicians in this testing, the article's Table 1 lists the pneumococcal vaccine serotypes in PCV7, PCV13, PCV15, PCV20, PCV21, and PPSV23.

The authors tested the hypothesis that PPSV23 could support a diagnosis of moderate-to-severe vaccine nonresponsiveness even if only 11 or 4 serotypes could be evaluated. Data were collected from patients' electronic medical records. PPSV23 responders were identified as people with a protective response to at least 70% of the serotypes analyzed. The authors compared the 23-serotype response (ie, all 23 serotypes in PPSV23) with responses to only the 11 unique serotypes not found in PCV13 or the 4 unique serotypes not found in PCV20. They found few false negatives and concluded that there is still diagnostic utility in administering PPSV23 in patients vaccinated with PCV13 or PCV20.

COMMENT: This manuscript offers practical advice and support for the continued use of pneumococcal polysaccharide vaccines in the assessment of patients with suspected antibody deficiency, even in patients previously vaccinated with PCVs. As it becomes more challenging to find pneumococcal polysaccharide vaccines, alternate diagnostic modalities are needed.

V.H.T.

Immunodeficiencies

Abdalgani M, Hernandez ER, Pedroza LA, et al. Clinical, immunologic, and genetic characteristics of 148 patients with natural killer cell deficiency. *J Allergy Clin Immunol.* 2025;155(5):1623-1634.

This was an observational study of 148 patients diagnosed with natural killer cell deficiency (NKD) across 3 institutions over a 16-year period. A small subset of people with inborn errors of immunity have NKD. Ten genes are currently linked to NKD: *ACTB*, *ELF4*, *FCGR3A*, *GATA2*, *GIN51*, *GIN54*, *IRF8*, *MCM4*, *MCM10*, and *RTEL1*.

The research program enrolled patients with clinical features of NKD and then performed NK cell cytotoxicity testing with the ^{51}Cr -release assay and NK cell immunophenotyping. Exome sequencing was performed in 99 patients, and a known or novel causative gene was identified in 29. The molecular diagnosis remained unsolved in 71% of patients who underwent exome sequencing. The patients' median age at enrollment was 13 years (range, 0-76 years), and 54% were female. Most (71%) patients had experienced at least 1 hallmark infection, the most frequent of which were herpes simplex virus (HSV) (32%) and Epstein-Barr virus (EBV) ● ● ●

(32%). Patients also experienced autoimmune, inflammatory, and malignant complications. About 30% had recurrent pneumonia, 32% had recurrent sinusitis, and 16% had recurrent otitis media. A malignancy was diagnosed in 10 patients; at the time of the publication, 7 patients were in remission and 3 had died. Six patients underwent hematopoietic stem cell transplantation.

Compared with age-matched healthy donors, patients had higher percentages of CD56^{bright} immature cells and lower percentages of CD16⁺ mature NK cells. They also had low CD19⁺ B cells (16%), low IgA (13%), and reduced pneumococcal titers (13%).

COMMENT: In this observational study, eligible phenotypes suggestive of NKD included recurrent, severe, or atypical viral infections and persistently abnormal NK cell quantity or function. Table 1 reviews cohort demographics. Figure 2 highlights index hallmark infections, of which EBV and HSV were most common. Figure 5 reviews the molecular diagnoses of 99 patients; 29% had a likely causative genetic mutation identified. Table 3 includes univariate analyses of clinical factors influencing patient outcomes: history of cytomegalovirus (CMV) infection, CMV viremia, having an NK cell percentage of less than 1%, having an identified genetic cause, and having autoimmune or autoinflammatory complications were associated with risk for severe outcomes.

T.G.C.

Tangye SG, Puel A. The Th17/IL-17 axis and host defense against fungal infections.

J Allergy Clin Immunol Pract. 2023;11(6):1624-1634.

CD4⁺ T cells mediate the body's immune response to pathogens. The Th17 subset of these cells, which produces IL-17, plays a role in immunity against fungal infections. People with an inborn error of immunity that disrupts the IL-17-mediated immune response develop chronic mucocutaneous candidiasis (CMC). The first genetic causes of isolated CMC to be identified were an autosomal dominant IL-17F deficiency and an autosomal recessive IL-17RA deficiency. In the first case, IL-17A/F signaling is impaired. In the latter case, it is abolished.

Specific cytokines and transcription factors are required for naïve CD4⁺ T cells to differentiate into Th17 cells. These include the cytokines IL-6, IL-21, and IL-23, and the transcription factors STAT3 and ROR γ t. Some patients with recessive mutations in genes encoding receptors for IL-12 and IL-23 develop recurrent fungal infections. Syndromic CMC occurs with several inborn errors of immunity. Of note:

- More than 85% of patients with autosomal dominant hyper-IgE syndrome, which is caused by a heterozygous dominant-negative variant of *STAT3*, have CMC.
- More than 80% of patients with ROR γ t deficiency develop CMC.
- Other genes linked to syndromic CMC in patients with inborn errors of immunity include *STAT1*, *JNK1*, and *CARD9*.

- CMC is common in patients with autoimmune polyendocrine syndrome type 1 (APS-1).

COMMENT: This review summarizes inborn errors of immunity associated with impaired IL-17-mediated immunity. Impaired Th17 immunity predominantly leads to CMC and can also result in increased risk for staphylococcal infections. Table 1 is high yield, reviewing the pattern of IL-17 production observed, the infectious disease profile, and autoimmune complications for different monogenic disorders. Figure 1 highlights that CMC can arise from monogenic disorders that present as part of a syndrome (pink text in the figure) or as an isolated phenomenon without other significant clinical features (blue text in the figure).

T.G.C.

Udemgba C, Pillay B, Shafer S, et al. IRF2BP2 deficiency: an important form of common variable immunodeficiency with inflammation.

J Allergy Clin Immunol. 2025;155(6):2052-2062.

"Patients with familial primary immunodeficiency with autoinflammatory manifestations should be evaluated for a heterozygous mutation in *IRF2BP2*," report Udemgba et al. Mutations in *IRF2BP2* have been found in patients with common variable immunodeficiency (CVID) and other immunodysregulatory conditions. *IRF2BP2* transcripts and protein are ubiquitously expressed in humans; levels are highest in bone marrow. Overexpression is implicated in cardiomyopathy and cancer.

Using extracted medical record data and whole exome or genome sequencing, the authors summarize the clinical and molecular immunophenotypes of 34 patients (15 female, 18 male, 1 gender not documented). Clinical data were available for 30 patients (13 female, 17 male), whose mean age was 26.6 years (range, 2-64 years). The patients' symptoms were sorted into the following clinical categories: primary immunodeficiency disease (PID; 91%), gastrointestinal (65%), inflammatory (57%), skin (50%), neuropsychiatric (50%), genitourinary (46%), pulmonary (44%), and general (41%). Selected findings are as follows:

- Most patients with an immunodeficient phenotype (eg, CVID) had recurrent sinopulmonary infections. Other infections included viral, fungal, and recurrent urinary tract infections.
- Most patients with gastrointestinal symptoms experienced chronic abdominal pain or constipation. Other symptoms included gastroesophageal reflux disease, colitis, Crohn disease, and cyclical vomiting.
- More than half (57%) of patients had rashes and inflammatory skin conditions like psoriasis, vitiligo, and eczema.
- Immunoglobulin levels were reduced in most patients: 77% had reduced IgG, 61% had reduced IgM, and 48% had reduced IgA.
- Among patients with radiographic imaging data, 69% had intrathoracic abnormalities and 59% had

intra-abdominal or gastrointestinal abnormalities (examples shown in Figure 4).

- Calcium flux in response to anti-immunoglobulin was impaired in the patients in whom this was tested, indicating a defect in B cell activation.

COMMENT: IRF2BP2 is a transcription factor with roles in IRF2 signaling as well as both immune cell and nonimmune cell differentiation, proliferation, and tumorigenesis. Figure 2 summarizes the clinical manifestations observed for different *IRF2BP2* mutations; the most common manifestation was PID, followed by gastrointestinal manifestations. Multiple immune defects were observed, including decreased memory B cells (Figure 5) with impaired immunoglobulin production (Figure 3). *IRF2BP2* mutations resulted in decreased repression of the NFAT pathway, resulting in increased proinflammatory signaling (Figure 7).

T.G.C.

Wijeyesinghe S, Chinen J. Gene therapy for inborn errors of immunity: current clinical progress. Ann Allergy Asthma Immunol. 2025;134(6):630-638.

Gene therapy protocols are being developed to correct inborn errors of immunity (IEs). In brief, hematopoietic stem cells (HSCs) are isolated from a patient, the gene defect is corrected in vitro, and functional gene copies are reinfused to the patient after mild myeloablation. Gene therapy includes viral-mediated strategies and gene-editing strategies. Genetic editing can address IEs caused by gain-of-function gene variants. Advantages of gene therapy over HSC transplantation (HSCT) protocols include that no donor is needed; thus, there is no risk of graft-versus-host disease and no need for immunosuppression.

One study of gene therapy for adenosine-deaminase-deficient severe combined immunodeficiency (ADA-SCID) reported a 100% survival rate for 131 patients (vs 79.6% for HSCT preceded by enzyme replacement therapy and 72.5% for HSCT without enzyme replacement therapy). Studies have shown that low-intensity myeloablation and stopping enzyme replacement therapy improves engraftment of corrected cells.

Gene therapy protocols for X-linked SCID to correct errors in *IL2RG* include therapy with lentiviral gene vectors with mild myeloablation and the use of CRISPR-Cas9 gene editing.

Artemis-deficient SCID is caused by variants of *DCLRE1C* and is characterized by impaired T cell and B cell development. One study of a lentiviral gene therapy in infants reported that of 4 patients followed up for at least 2 years, all had discontinued immunoglobulin replacement therapy.

Other IEs for which gene therapy is being developed include:

- Recombination-activating gene (RAG) 1- and RAG2-SCID
- IL7RA-SCID
- Wiskott-Aldrich syndrome
- Chronic granulomatous disease

- Leukocyte adhesion deficiency type 1

- X-linked agammaglobulinemia

Protocols continue to be improved to address the risk for insertional mutagenesis.

COMMENT: Table 1 compares general features of HSCT and gene therapy. Figure 1 reviews the general steps involved in gene therapy protocols for monogenic immunodeficiencies. Table 2 reviews the different IEs for which gene therapy is being investigated in preclinical and clinical trials. Clinical trials using lentiviral vectors and gene editing have been undertaken (Table 3). This field is rapidly changing; gene therapies for Wiskott-Aldrich syndrome and leukocyte adhesion deficiency type 1 are now FDA approved but were not at the time of this publication.

T.G.C.

Eosinophilic or Gastrointestinal Disorders

Caminati M, Maule M, Bagnasco D, et al. Profiling blood hypereosinophilia in patients on dupilumab treatment for respiratory conditions: a real-life snapshot.

J Allergy Clin Immunol Pract. 2025;13(6):1367-1374.

Some dupilumab-treated patients experience an increase in blood eosinophil count (BEC). These authors report real-world data for 195 dupilumab-treated patients with asthma and/or chronic rhinosinusitis with nasal polyps (CRSwNP). Patients were treated at 13 Italian referral centers for severe asthma and received 300 mg dupilumab subcutaneously every 2 weeks. BEC was measured every 3 months for 30 months. Eosinophilia was defined as BEC from 0.5 to 1.5 x 10⁹ cells/L and severe hypereosinophilia as BEC greater than 5 x 10⁹ cells/L.

Nearly half of patients had at least one chronic comorbidity; the most common were gastroesophageal reflux, hypertension, and osteoporosis. Twenty-nine patients (about 15%) developed hypereosinophilia (BEC between 1.5 and 5 x 10⁹ cells/L). Only 2 of the patients in whom BEC increased developed severe hypereosinophilia. Patients with comorbidities had a 4 times greater risk of developing symptoms (95% CI, 1.48-14.25). For 16 patients (about 15%), eosinophilia triggered a medical action: 14 were prescribed oral corticosteroids and in 2 the dupilumab schedule was extended at 28-day intervals. Dupilumab was stopped in 14 patients in whom blood eosinophils increased.

Given that the median time to peak eosinophilia was 6 months, the authors note that eosinophil assessment should not be limited to the initial treatment stage.

COMMENT: This prospective observational study evaluated the incidence, clinical course, and risk factors for eosinophilia in patients with CRSwNP and severe asthma • • •

treated with dupilumab. Among the 195 participants, who were almost exclusively White, 39.5% had baseline blood eosinophilia. Following treatment, 55% experienced a rise in BEC, and about 15% developed hypereosinophilia. Baseline eosinophilia was a predictor: patients with a BEC between 0.5 and 1.5×10^9 cells/L were 3.3 times as likely to develop hypereosinophilia as were those with a BEC $<0.5 \times 10^9$ cells/L. Hypereosinophilia developed after a median of 6 months. The most common co-occurring symptoms were asthma exacerbations followed by myalgia. Most patients experienced a resolution of eosinophilia after a median of 9 months.

S.J.

Lozano-Ojalvo D, Chen X, Kazmi W, et al. Differential T follicular helper cell phenotypes distinguish IgE-mediated milk allergy from eosinophilic esophagitis in children. *J Allergy Clin Immunol.* 2025;155(3):909-922.

The article reports that IgE-mediated milk allergy is associated with milk-specific $T_{FH}13$ (T follicular helper) cells, whereas eosinophilic esophagitis (EoE) is associated with milk-specific helper T cells that produce IL-10. To better distinguish IgE-mediated food allergy and EoE, the authors analyzed $CD4^+$ T-cell phenotypes in peripheral blood or esophageal biopsy samples using spectral flow cytometry. The study sample included a control group ($n = 35$; mean age, 11.4 years), children with active EoE ($n = 31$; mean age, 11.2 years), children with EoE in remission ($n = 21$; mean age, 11.6 years), and children with IgE-mediated milk allergy ($n = 10$; mean age, 14 years).

Children with IgE-mediated milk allergy had higher levels of milk- and casein-specific IgE. Children with active EoE had higher levels of β -lactoglobulin-specific IgG4. Children with IgE-mediated milk allergy and those with active EoE had more milk-responsive memory $CD4^+$ T cells in circulation. These groups also produced more milk-induced IL-2. Children with IgE-mediated milk allergy had a significantly increased response of the type 2 cytokines IL-4, IL-5, IL-9, and IL-13 in response to stimulation with milk, whereas children with EoE did not. In children with IgE-mediated milk allergy and children with EoE, T_H2A cell levels were elevated compared with the control group. Within the milk-responsive T_{FH} subset, $T_{FH}13$ cells were predominant in children with IgE-mediated milk allergy, whereas IL-10-producing T_{FH} cells were predominant in children with EoE.

Although both children with IgE-mediated milk allergy and those with EoE had elevated numbers of T_H2A cells, the study found a dichotomy in the circulating T_{FH} cell phenotype.

COMMENT: The authors investigated the distinct $CD4^+$ T-cell mechanisms from cow's milk as a trigger for IgE-mediated milk allergy and EoE despite both being associated with type 2 immunity. They found milk-responsive T_{FH} cell subsets

with distinct phenotypes. $T_{FH}13$ cells predominated in milk allergy, promoting IL-4/IL-13 production and IgE responses, whereas T_{FH} cells producing IL-10 predominated in EoE. IL-10+ T_{FH} cells produce low levels of IL-4 that may result in low-affinity milk-specific IgE that is not clinically significant. Additionally, IL-10+ T_{FH} cells in the periphery and IL-10+IL-21+ T cells in the esophagus may drive systemic and local IgG4 production.

S.J.

McGowan EC, Wright BL, Ruffner MA, et al. Eosinophilic esophagitis: an allergy and immunology perspective on the updated guidelines. *J Allergy Clin Immunol.* 2025;156(2):252-258.

Guidelines on the diagnosis and management of eosinophilic esophagitis (EoE) were updated in 2025 by the American College of Gastroenterology and are summarized in Table 1. EoE is diagnosed by the presence of symptoms of esophageal dysfunction and 15 or more eosinophils per high-power field on esophageal biopsy and the exclusion of other conditions associated with esophageal eosinophilia. Initial treatments include proton pump inhibitors (PPIs), swallowed esophageal topical steroids, and elimination diets. I-SEE (Index of Severity for EoE) is a new composite assessment tool that can be used in a mobile app to evaluate treatment response. The guidelines recommend against the use of currently available allergy tests (skin-prick, serum IgE, serum IgG, patch testing) to direct elimination diets in patients with EoE. Skin testing may have a role in diagnosing and managing comorbid IgE-mediated food allergy, which affects about one-quarter of patients with EoE, and for food reintroduction during elimination diets. Other roles for skin testing are in diagnosing and managing comorbid allergic rhinitis and asthma.

Figure 1 summarizes key roles of allergists in diagnosing and managing EoE. Many patients with allergy have undiagnosed EoE. The authors advise allergists to "routinely ask about these subtle symptoms of esophageal dysfunction." Additional research is needed to clarify why some patients with IgE-mediated food allergy treated with oral immunotherapy develop EoE. Allergists may play an increasing role in monitoring these patients, such as with the esophageal string test or transnasal endoscopy.

COMMENT: Key 2025 EoE guideline updates:

- Treat both inflammatory and fibrostenotic disease.
- One-food (dairy) elimination diets may be as effective as 4- and 6-food elimination diets.
- Dupilumab is recommended for patients aged 1 year or older with PPI-refractory EoE and may be considered earlier when another indication exists.
- Treatment response should be assessed using symptoms, endoscopy (8-12 weeks after most therapies; 12-24 weeks after dupilumab), and histology, with the I-SEE tool helping to classify disease severity.

Role of allergists:

- Screen for underrecognized EoE.
 - Diagnose and treat other atopic conditions, especially comorbid IgE-mediated food allergy, pollen food syndrome, and allergic rhinitis.
 - Counsel regarding elimination diets and role of food allergy testing.
- S.J.

Wechsler ME, Nair P, Terrier B, et al. Benralizumab versus mepolizumab for eosinophilic granulomatosis with polyangiitis. *N Engl J Med.* 2024;390(10):911-921.

MANDARA (NCT04157348; funded by AstraZeneca) is a phase 3, double-blind, randomized noninferiority trial that compared benralizumab to mepolizumab in 140 adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA). Mepolizumab binds IL-5, whereas benralizumab binds the IL-5 receptor α subunit (IL-5R α). Patients in the 52-week trial were assigned 1:1 to 30 mg benralizumab (1 injection) or 300 mg mepolizumab (3 injections of 100 mg each) every 4 weeks. Patients continued their oral corticosteroid doses, which were tapered at a Birmingham Vasculitis Activity Score (BVAS) of 0. Remission was defined as a BVAS of 0 and an oral glucocorticoid dose of 4 mg or less per day.

The patients' mean age was 52 years, and 60% were women. All had asthma and blood eosinophilia. Their mean oral glucocorticoid dose at baseline was 11 mg/d (median, 10 mg/d; range, 5-40 mg/d).

Remission was achieved within 24 weeks and maintained for 52 weeks by 42% of benralizumab-treated patients and 36% of mepolizumab-treated patients (difference, 6 percentage points; 95% CI, -9 to 20). About 30% of both groups experienced a relapse. A total of 68% of the benralizumab group and 70% of the mepolizumab group achieved an oral glucocorticoid dose of 4 mg or less during the last 4 weeks of the trial. Blood eosinophil counts decreased in both groups. The most often reported serious adverse events were COVID-19 (1 patient in each group) and prostate cancer (2 patients in the mepolizumab group).

COMMENT: The primary end point of the MANDARA trial, which was remission at weeks 36 and 48, was achieved in 58% vs 56% or benralizumab- vs mepolizumab-treated patients, respectively, achieving noninferiority but not superiority. Secondary end points suggest similar accrued and sustained remission duration and time to relapse. In the last 4 weeks of the trial, in comparing benralizumab to mepolizumab treatment groups, glucocorticoid use was reduced by 50% or more in 85% vs 74% (11% difference) and completely withdrawn in 41% vs 26% (16% difference). Both had similar safety profiles and rare, serious adverse events.

S.J.

Emerging National Health Priorities

Cooper D, Holmboe ES. Competency-based medical education at the front lines of patient care.

***N Engl J Med.* 2025;393(4):376-388.**

Competency-based medical education (CBME) is an alternative to the traditional, time-based approach to medical education. CBME is an outcomes-focused model that provides a possible solution to the varying skill levels of trainees upon completion of traditional medical education.

In the CBME model, trainees exit the program when they demonstrate competency, not at a fixed time point. Assessment occurs through direct observation of trainees and the provision of "frequent and immediate" feedback rather than through summative assessments. One Canadian study of family medicine trainees reported that CBME "provided opportunities for early course correction," thus reducing the number of residents with flagged deficiencies at the time of promotion. The responsibility for training is shared. For example:

- Education leaders like program directors and associate deans contribute to developing curricula and setting milestones.
- Faculty sit on clinical competency committees, make decisions about trainee readiness, and provide feedback.
- Program directors work with trainees to develop learning plans and provide progress reports.
- Clinician educators observe trainees and provide feedback and coaching.
- Trainees are placed at the center of the learning process and can provide feedback on the strengths and weaknesses of the program.

As an illustration, Figure 3 describes how a trainee would progress through various competency milestones on the path to achieving proficiency in one of the American Board of Pediatrics' core professional activities. Challenges in implementing CBME include a fragmented learning environment, siloed training environments, and the time needed to support individual learners. The authors argue that rather than being resource intensive, CBME "should be considered a return on investment from the perspective of patients and populations."

COMMENT: The concept of CBME revolves around blending educational and health care outcomes instead of treating them as separate entities. This form of training requires a multidisciplinary approach where educational leaders provide direction and resources to clinician educators while regularly assessing individual progress of trainees. By evaluating various domains based on competency milestones, learners may follow different learning curves. The completion of the training program may vary widely from trainee to trainee based on when they reach the desired competency thresholds.

S.R.J.

Gilbert KM, McLaughlin HM, Farmer JR, et al. Disparities in genetic testing for inborn errors of immunity. *J Allergy Clin Immunol Pract.* 2025;13(2):388-395.

Gilbert et al studied the socioeconomic, geographic, and racial characteristics of patients undergoing genetic testing for inborn errors of immunity (IEIs) and the effects of a free sponsored testing program on testing uptake. The study was a retrospective cohort analysis of data in a national claims database and from a clinical genetic testing laboratory. Data for patients who underwent free genetic testing were from the navigateAPDS program sponsored by Pharming Healthcare Inc. A comparison group underwent testing covered by their health insurance plan or paid for out of pocket.

The claims database included 18,603 patients with an IEI diagnosis. Most lived in urban areas (90%) and in predominantly White neighborhoods (77%). Patients living in areas of greater deprivation, rural areas, and predominantly non-White neighborhoods were less likely to undergo genetic testing. 6681 patients underwent testing as part of the navigateAPDS program. Patients who received free testing were more likely to live in areas of greater deprivation. They were also majority White (90%); only 4% of the cohort who underwent free testing were Black. Relative to the US population as a whole, American Indian or Alaska Native, Asian, Black, and Hispanic patients were underrepresented in both testing cohorts regardless of payment type. Although nearly one-quarter of the patients for whom an IEI was listed as a contributing cause of death were Black, Black patients made up only 4% of the sponsored testing cohort and 8% of the non-sponsored testing cohort. Removing the barrier of cost alone was not sufficient to address existing racial disparities in use of genetic testing.

COMMENT: This retrospective study sought to understand whether disparities exist in the uptake of genetic testing for IEIs. Not surprisingly, among individuals who received sponsored genetic testing, 88% lived in urban areas and 90% were White, which were both overrepresentations. No-charge genetic testing programs have been proposed as a solution to reduce disparities in testing; however, this study revealed that historically excluded racial groups remained underrepresented even in this free program.

S.R.J.

Han YY, Celedón JC. The effects of violence and related stress on asthma. *Ann Allergy Asthma Immunol.* 2024;133(6):630-640.

Han and Celedón review evidence for a causal relation between exposure to violence and asthma or worse asthma outcomes. At the individual level, cross-sectional studies (summarized in Table 1) report that witnessing or experiencing violence at home or school is associated with asthma in school-aged children. One study reported that bronchodilator responsiveness is lower in children who experienced more

violence-related distress in the previous 6 months. Violence-related distress has also been reported to lower growth rates in FEV₁ and forced vital capacity.

Childhood maltreatment may be associated with the odds of developing asthma. One cross-sectional study reported that any childhood maltreatment was associated with 22% greater odds of current asthma, and that nearly one-third of the effect was explained by lifetime generalized anxiety disorder and/or major depressive disorder. Chronic distress caused by bullying and cyberbullying in school-aged children has been linked to increased odds of asthma ranging from 27% to 59%.

At the intrafamilial level (summarized in Table 2), odds of asthma are increased in offspring of mothers with a history of interpersonal violence, domestic violence, or interpersonal trauma. Associations have also been reported with lung function in infants and recurrent wheeze in toddlers.

Chronic stress and exposure to violence can have direct effects on physiology and indirect effects on health behaviors. Physiological mechanisms include chronic hypothalamic-pituitary-adrenal activation, immune modulation, and genetic and epigenetic modification. Indirectly, chronic stress and exposure to violence can reduce dietary and sleep quality, reduce physical activity, increase overweight and obesity, and increase smoking and substance use. Modifiers of these effects include age, sex, socioeconomic status, air pollution, comorbidities, and genetic predisposition.

COMMENT: The authors explore initial data on an increased prevalence of type 2 asthma biomarkers and violence-related distress in the past 6 months, specifically in Puerto Rican youth. A meta-analysis from 4337 mother-child dyads revealed maternal report of child maltreatment before the age of 18 was associated with 1.54 increased odds of asthma in the offspring. This review highlights the need for allergists to regularly screen for violence-related mental illness in children and adults through validated tools such as the Generalized Anxiety Disorder-7 questionnaire.

S.R.J.

Konstantinou GN, Anderson WC 3rd, Bagkis E, et al. Artificial intelligence-driven wearable and connected technology for allergy: real-time monitoring and predictive management for personalized care. *J Allergy Clin Immunol Pract.* 2025;13(11):2903-2913.

Artificial intelligence (AI)-driven technologies can support real-time monitoring and personalized alerts in allergy care. Tools include wearables like smartwatches and connected devices like digital inhalers. The main classes of devices are (1) personal air-quality monitors, (2) portable food-allergen biosensors, (3) physiologic monitoring wearables, (4) behavioral monitoring devices, and (5) medication adherence devices. Table E1 provides a representative listing of marketed devices, including manufacturers, regulatory status, and supporting publications.

Personal air-quality monitors report pollutants and particulates that may aggravate allergic symptoms. Personal devices for testing food for the presence of allergens are not yet commercially available. Physiologic variables monitored by wearables include heart rate, oxygen saturation, skin temperature, and respiratory acoustics. An AI-enabled accelerometer worn on the chest was reported to detect asthmatic wheezing with greater accuracy than a stethoscope. Behavioral monitoring can link measures like actigraphy and atopic dermatitis severity or sleep quality and asthma control. Feedback provided by smart inhalers may improve adherence.

Predictive tools aim to forecast allergy-related outcomes like asthma exacerbations, allergic rhinitis symptoms, and food allergy risk. Wearable intervention devices include nasal acoustic therapy wearables, which use sound vibrations to reduce nasal congestion (an over-the-counter device has FDA approval), and epinephrine delivery wearables (still in development). Limitations include data privacy concerns, regulatory status, and technical limitations like motion artifacts, loss of signal, and inconsistent network connections.

COMMENT: The future of wearable technology is vast, including the ability to track patients' biological signals, detect environmental exposures, monitor patient behaviors, log inhaler use and technique, and trigger therapy in response to allergic events. Concerns over bias and fairness persist, such as the overestimation of oxygen saturation in people with darker skin leading to occult hypoxemia. This information can then propagate bias when such data are fed into AI pipelines. Many regulatory and privacy hurdles remain, and the Food, Drug, and Cosmetic Act in the United States created guardrails for future implementation.

S.R.J.

Pongdee T, Brunner WM, Kanuga MJ, et al. Rural health disparities in allergy, asthma, and immunologic diseases: the current state and future direction for clinical care and research.

J Allergy Clin Immunol Pract. 2024;12(2):334-344.

Mortality from the 5 leading causes of death (heart disease, cancer, unintentional injury, chronic lower respiratory disease, and stroke) is greater in rural US residents than in nonrural residents. Life expectancies can differ by up to 2 years. Social determinants of health (SDHs) are associated with health disparities between rural and urban regions. SDHs include economic stability, access to education, and neighborhood environments. These influence environmental, behavioral, and biological factors that in turn affect health outcomes. Rural areas have less access to primary care, dental, and mental health services, and since 2010 have lost many hospitals.

More data are needed on the impact of differential access to allergen immunotherapy between rural and urban

patients. Neither asthma prevalence nor outcomes differ consistently between rural and urban areas. Rather, asthma incidence is influenced by interactions among factors and neighborhood characteristics. Data are lacking on disparities in atopic dermatitis care in rural populations. Studies have reported that food allergy diagnoses have increased more in rural areas than in urban areas and that rural patients with food allergy have greater allergy-related anxiety.

The HOUSES Index is a measure of SDHs. Health care organizations can use the index to plan community engagement and outreach. The Asthma-Guidance and Prediction System is a clinical decision support tool that provides up-to-date information on asthma management.

COMMENT: While no standard definition exists, about 15% to 20% of the US population lives in rural or nonmetropolitan areas. Over the past 3 decades, the difference in the age-adjusted death rate between rural and urban areas has increased from 7% higher in rural areas in 1999 to 20% higher in 2019. Factors explaining this discrepancy include the lack of access to health care in many rural communities. This lack is amplified by a large migrant agricultural workforce in rural areas, who may have greater difficulty establishing relationships with health care providers and maintaining treatment regimens. As clinicians, it is our responsibility to be aware of these obstacles and provide the needed support to our rural patients.

S.R.J.

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