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

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## Using Azithromycin to Achieve Asthma Remission

Azithromycin is a macrolide antibiotic, a class of antibiotics being studied for the treatment of obstructive airway diseases such as asthma. In contrast with biologics, azithromycin is effective for both Th2 high and Th2 low asthma. These authors sought to answer whether patients with persistent uncontrolled asthma could achieve remission by adding azithromycin to their standard therapy.

The Asthma and Macrolides: the Azithromycin Efficacy and Safety (AMAZES) randomized clinical trial was conducted at 8 sites in Australia in adults with persistent uncontrolled asthma. The treatment group received 500 mg azithromycin 3 times per week as add-on therapy for 48 weeks; the control group received placebo. *Remission* was defined clinically as no exacerbations and no use of oral corticosteroids in the previous 6 months as evaluated at 12 months and a score of 1 or less on the 5-item Asthma Control Questionnaire (ACQ-5) at 12 months.

This article presents a secondary analysis of study data for 355 participants (168 in the treatment group and 167 in the control). The participants' mean ACQ-5 score at baseline was 1.6. At follow-up, more patients treated with azithromycin vs placebo achieved clinical remission (51% vs 39%). This was true also for clinical remission plus lung function criteria and in sensitivity analyses using more stringent ACQ-5 criteria. In the subgroup analysis of patients with eosinophilic, neutrophilic, or paucigranulocytic airway inflammation, about half of participants in the treatment group achieved clinical remission. The number needed to treat was 9.

As better therapies for asthma become available, attention has shifted to achieving disease remission. In this study, adding azithromycin to standard therapy allowed a significant number of patients to achieve this treatment goal.

**COMMENT:** Asthma remission remains a major therapeutic goal. While azithromycin has been recommended • • •

### FEATURE ARTICLES



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- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of Asthma
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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as add-on therapy for severe refractory asthma in various guidelines, it has often been overlooked since the introduction of asthma biologics. This is the first study to evaluate remission as an outcome for macrolides. A key finding was that remission was obtained regardless of the underlying asthma phenotype (eosinophilic, neutrophilic, or paucigranulocytic). Azithromycin has an excellent overall safety profile and is generally cost-effective compared with biologic agents. Allergists should consider its use in patients with refractory asthma as add-on therapy before or in addition to biologics.

S.R.J.

Thomas D, McDonald VM, Stevens S, et al. Effect of azithromycin on asthma remission in adults with persistent uncontrolled asthma: a secondary analysis of a randomized, double-anonymized, placebo-controlled trial.
Chest. 2024;166(2):262-270.

Keywords: antibacterial agents, asthma, azithromycin

## Neighborhood Air Pollution Contributes to Disparities in Asthma Care

How do neighborhood-level differences in air pollution affect asthma care? Knowing that air pollution levels at the ZIP code and county levels affect acute care use, these authors further explored the associations of air pollution gradients within neighborhoods with emergency department (ED) visits for asthma care in 2016 and 2017. Four air pollutants were studied: particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), $PM_{10}$, nitrogen dioxide, and sulfur dioxide, concentrations of which were obtained from the Center for Air, Climate, and Energy Solutions. The authors used generalized linear models to study the association of air pollution with incidence rates of asthma-related ED care.

The study included 5 counties in the Austin, Texas, area. Although levels of air pollution were low compared with other major US cities, average concentrations of $PM_{2.5}$, $PM_{10}$, and sulfur dioxide were associated with an increase in ED visits for asthma care. Every 1-SD increase in $PM_{10}$ was associated with an average 30% higher rate of ED use. Median concentrations of the pollutants were highest for Black residents, followed by Latinx residents. The percentage of Black and Latinx residents within a neighborhood predicted ED visit rates, and these associations were attenuated when accounting for neighborhood air pollution.

The rate of use of acute care services for asthma care is associated with local air pollution. The findings suggest that neighborhood-level differences in air pollution contribute to disparities in asthma morbidity.

**COMMENT:** Racial and ethnic disparities in asthma acute care use have been described in urban environments. The role of air pollution as a contributor to these disparities across neighborhoods has not been well characterized. In this study, after control for neighborhood-level variations in air pollution exposure and socioeconomic and housing covariates, the association between asthma-related ED visits and Black or Latinx neighborhood resident share was decreased by 24% to 32%. This suggests that community social determinants of health impacting outdoor air quality are a significant contributor to previously observed racial and ethnic disparities in asthma-related ED visits and may be a target for future public health interventions.

T.G.C.

Chambliss SE, Matsui EC, Zárate RA, et al. The role of neighborhood air pollution in disparate racial and ethnic asthma acute care use. Am J Respir Crit Care Med. 2024;210(2):178-185.

Keywords: air pollution, asthma, ethnicity, neighborhood characteristics

## Quality of YouTube for Asthma Education Depends on the Narrator

Patients must follow several steps to use inhalers correctly and may turn to social media platforms like YouTube for tutorial videos. However, previous studies have raised concerns about the accuracy of YouTube videos for patient education. These investigators from Turkey assessed the quality and content of 178 YouTube videos on inhaler use. All the videos evaluated were in Turkish.

The quality and content of the videos were assessed by using the Global Quality Score, the JAMA Benchmark Criteria, and the Inhaler Application Checklist. Other video features such as time since upload and number of views and comments were also recorded. Video narrators were grouped into 4 categories: doctor, nurse, unspecified, and patient.

The mean Global Quality Score of the videos studied was 3.7 (on a scale of 1-5, with higher scores indicating higher quality). The mean JAMA score was 2.2 (on a scale of 0-4). Both quality scores were negatively associated with number of views. Videos narrated by patients had more views, likes, and comments, but those narrated by nurses or doctors had higher quality scores than videos narrated by patients or anonymous narrators. Quality scores were higher for videos uploaded by professional organizations than for videos uploaded by individuals. Videos uploaded by individuals were more likely to skip procedural steps than were videos uploaded by professional organizations.

The videos reviewed had been viewed more than 20,000 times but were of "medium quality" according to Global Quality Score and the JAMA Benchmark Criteria. The authors recommend counseling patients about the reliability of online health care information.

**COMMENT:** For those of us wondering how to improve our patients' understanding of proper inhaler use, this study offers a glimpse of hope regarding how to reach patients. The use of YouTube videos was helpful when medical professionals were involved. This is another reminder for allergists and immunologists to "own the space" as asthma experts. Concerns about proper administration of asthma medications may be addressed by making videos with accurate steps in use of asthma inhalers. This may be a way to reach our patients.

V.H.T.

Canbolat O, Dogan Aktas AB, et al. Evaluation of the quality and content of YouTube videos as an educational resource in developing patients' inhaler use skills. J Asthma. 2024;61(9):1006-1014.

Keywords: asthma, patient education, social media

## Real-World Data on Benralizumab for Severe Eosinophilic Asthma

Benralizumab is a biologic antibody that acts on the interleukin-5 receptor and has long-term benefits in patients with uncontrolled severe eosinophilic asthma (SEA). Data are lacking, however, on the real-world use of benralizumab, particularly in patients previously prescribed another biologic. The XALOC program was established to address this gap using data from 5 countries: Italy, Portugal, the United Kingdom, Spain, and Canada. This article reports a 48-week integrated analysis of real-world benralizumab efficacy in adults with SEA.

Patients were grouped according to whether they had previously received a biologic treatment for asthma in the 12-month baseline period. Outcomes assessed included number of exacerbations, asthma symptom control, and pre- and postbronchodilator $FEV_1$.

About 38% of the 1002 patients included in the analysis had previously received omalizumab, mepolizumab, or reslizumab. The relative reduction in the annualized exacerbation rate from baseline to week 48 with benralizumab was about 88% in biologic-naïve patients, 75% in omalizumab-experienced patients, and 69% in mepolizumab-experienced patients. The mean daily maintenance oral corticosteroid dose was reduced by 63% and by 35% in biologic-naïve and biologic-experienced patients, respectively. About 56% of biologic-naïve patients and 37% of biologic-experienced patients completely eliminated their use of maintenance oral corticosteroids. Overall, 78% of patients were still taking benralizumab at 48 weeks. Among those who discontinued treatment, most stopped in the 7- to 12-month time frame because of lack of efficacy.

The study findings suggest that benralizumab is effective in patients previously treated with mepolizumab or omalizumab.

**COMMENT:** Direct head-to-head randomized controlled trials comparing different biologic treatments are lacking, and numerous approaches have been used to draw indirect comparisons of efficacy. One approach is the use of real-world studies to evaluate the efficacy of biologics in biologic-experienced patients (patients with poor control of asthma while on a different biologic). In this multinational real-world study, benralizumab was effective in significantly decreasing exacerbations and requirement for maintenance systemic steroids in both biologic-naïve and mepolizumab- or omalizumab-experienced patients. However, significant caution is needed when interpreting the findings as providing strong evidence of superior efficacy because of the reduced rigor of real-world studies and the significant conflict of interest given AstraZeneca's funding of the study.

T.G.C.

Jackson DJ, Pelaia G, Emmanuel B, et al. Benralizumab in severe eosinophilic asthma by previous biologic use and key clinical subgroups: real-world XALOC-1 programme. Eur Respir J. 2024;64(1):2301521.

Keywords: adrenal cortex hormones, asthma (adult), benralizumab

## Omics Biomarkers to Predict Improvement in Asthma With Biologic Agents

Omalizumab is an anti-IgE monoclonal antibody that is used to treat patients with severe asthma, but allergists currently cannot predict which patients will most benefit in the long term. This study aimed to identify omics biomarkers in breath, blood, sputum, and urine to predict which patients would improve with omalizumab treatment. The open-label, real-world study of patients with severe asthma measured more than 1400 omics variables. The predictive value of each biomarker was compared with standard biomarkers and with Global Evaluation of Treatment Effectiveness (GETE) scores, a clinical tool based on physician assessment.

At 16 weeks, 63% of the study sample were classified as early responders according to GETE score. Of the participants who completed phase 2 of the study (weeks 16-52), 71% were late responders according to a reduction in acute exacerbations of 50% or more. Breathomics and plasma lipidomics biomarkers predicted early and late responses. Exhaled breath biomarkers predicting early improvement included the volatile organic compounds benzothiazole, acetophenone, and methylene chloride. Volatile organic compounds predicting exacerbation response included 2-ethyl-1-hexanol and toluene. Four triglycerides predicted early response. The other omics platforms had weak predictive value. Several of the biomarkers identified could also differentiate between participants with severe or mild-to-moderate asthma.

The authors suggest that further validation of the identified biomarkers focus on breathomics, an easy-to-apply platform with easier sample collection.

**COMMENT:** Precision medicine, according to the Food and Drug Administration, aims "to target the right treatments to the right patients at the right time." For uncontrolled T2-high severe asthma, general parameters help guide clinicians to select appropriate patients who may benefit from specific biologic therapies but remain unrefined. These authors report 5 volatile organic compounds (through "breathomics") and 5 plasma lipid biomarkers that predicted a decrease in exacerbations of 50% or more. These findings will require confirmation and validation through larger studies. Whether the biomarkers identified will pan out in clinical practice remains to be seen, but I expect that we will get better at "precisely" prescribing biologics over the next 5 years.

T.G.C.

Djukanović R, Brinkman P, Kolmert J, et al; SoMOSA study team; U-BIOPRED study team. Biomarker predictors of clinical efficacy of the anti-IgE biologic omalizumab in severe asthma in adults: results of the SoMOSA study. Am J Respir Crit Care Med. 2024;210(3):288-297.

Keywords: asthma (adult), biomarkers, omalizumab

## FeNO as a Biomarker of Improved Lung Function With Dupilumab

Fractional exhaled nitric oxide (FeNO) is an easily tested biomarker that can predict response to biologic therapies in patients with asthma. FeNO reflects asthma severity and interleukin (IL)-4/IL-13-mediated inflammation. Previous analyses of data from the LIBERTY ASTHMA QUEST trial showed that FeNO could predict severe exacerbations better than blood eosinophil levels and that higher baseline FeNO was associated with greater clinical benefit in patients treated with dupilumab. This additional post hoc analysis of QUEST data further explored associations of FeNO with annualized severe exacerbation rates and changes in lung function.

QUEST was a phase 3 trial of dupilumab in patients with moderate to severe asthma. This analysis of the intention-to-treat population pooled data from the primary trial for patients receiving 200 or 300 mg dupilumab.

FeNO levels declined rapidly in the dupilumab group during the first 2 weeks of treatment and then more gradually from week 2 to 52. FeNO did not change significantly in the placebo group. Blood eosinophils increased until week 12 and then returned to baseline from week 12 to 52. The median fold change in FeNO from baseline to week 52 was 0.6 in the dupilumab group and 0.9 in the placebo group. The median fold change in blood eosinophils was 0.9 in both groups. The annualized exacerbation rate remained low in the dupilumab group and was not associated with fold change in FeNO. By contrast, the mean change in prebronchodilator $FEV_1$ was inversely associated with fold change in FeNO. The greater the reduction in FeNO, the greater the benefit of dupilumab on lung function.

These findings expand on the authors' previous analyses by showing that not only baseline FeNO but also fold change in FeNO at 52 weeks can predict improvement in lung function with dupilumab treatment.

**COMMENT:** This study showed that dupilumab decreased FeNO early in treatment and sustained this effect over the course of 1 year. Importantly, the reduction in FeNO correlated with improvement in $FEV_1$ and may be a biomarker to assess response to dupilumab. Establishing biomarkers for the available asthma biologics may ease decision-making about biologic therapeutic response and when to consider an alternative.

S.M.K.

Pavord ID, Casale TB, Corren J, et al. Dupilumab reduces exacerbations independent of changes in biomarkers in moderate-to-severe asthma. J Allergy Clin Immunol Pract. 2024;12(7):1763-1772.

Keywords: asthma, dupilumab, eosinophils

## A New Biomarker for Allergic Bronchopulmonary Aspergillosis

Fractional exhaled nitric oxide (FeNO) is used as a biomarker of Th2 inflammation in asthma. Like asthma, allergic bronchopulmonary aspergillosis (ABPA) involves a Th2

inflammatory response. These authors thus investigated whether FeNO could serve as a biomarker in patients with ABPA to predict prognosis and guide glucocorticoid therapy.

The findings were from 2 studies performed at a hospital in Shanghai: one retrospective study (2014–2017) and one prospective observational study (2018–2021). In the retrospective study, patients with ABPA were divided into groups according to disease control. FeNO was higher in patients with poorly controlled disease. Enrolled patients in the prospective study were divided into groups according to baseline FeNO (high or low). The rate of relapse or exacerbation was higher in the high-FeNO group than in the low-FeNO group (56% vs 24%). The median duration of oral glucocorticoid treatment was lower in the low-FeNO group (8 months vs 13 months in the high-FeNO group). The time between glucocorticoid withdrawal and the next relapse or exacerbation was shorter in the high-FeNO group. Baseline FeNO was positively correlated with *Aspergillus fumigatus*–specific IgE and IgG, blood eosinophil count, and eosinophil percentage. Receiver operating characteristic curve analysis showed a higher area under the curve for the combination of total IgE and FeNO than for the individual indexes.

FeNO has value for assessing the prognosis of patients with ABPA and for guiding glucocorticoid treatment. Combining FeNO with IgE may improve the accuracy of assessment in these patients.

**COMMENT:** This study found that patients with higher baseline FeNO levels require significantly longer glucocorticoid treatment and are at higher risk for relapse following glucocorticoid discontinuation. Baseline FeNO levels were not correlated with total IgE, which is currently a primary biomarker in determining glucocorticoid dosing and duration. Taken together, this suggests that incorporating baseline FeNO levels may improve prognostication in ABPA. It must be noted that none of the patients in the study had cystic fibrosis, somewhat limiting the generalizability of the findings. It will be interesting to see whether FeNO monitoring can additionally help guide treatment over time.

I.M.O.

Zhang LS, Wu YF, Lu HW, et al. Fractional exhaled nitric oxide, a potential biomarker for evaluating glucocorticoids treatment and prognosis in allergic bronchopulmonary aspergillosis.
Ann Allergy Asthma Immunol. 2024;133(2):168-176.

Keywords: aspergillosis, biomarkers, glucocorticoids, IgE, IgG

## Possible Biomarker of Tolerance During Peanut Oral Immunotherapy

Biomarkers of response to oral immunotherapy (OIT) for peanut allergy are needed. These authors previously characterized conformational epitopes of the peanut allergen Ara h 2, which they identified as 1.1, 1.2, 2, and 3. In this study, the authors assayed antibody binding to these epitopes during peanut OIT. Samples were from participants of 2 clinical trials of peanut OIT. Passive cutaneous anaphylaxis studies were performed in mice.

Using IgG-depleted serum from participants before and after OIT, the authors found that each of the monoclonal antibodies (mAbs) recognizing different Ara h 2 epitopes inhibited serum IgE similarly. Experiments measuring the additive effect of the different mAbs showed that serum IgE was inhibited most by the combination of neutralizing mAbs recognizing epitopes 1.2 and 3. In samples from patients undergoing OIT, neutralizing antibodies inhibited serum IgE binding to Ara h 2 more than did non-neutralizing antibodies. Concerning IgG subclasses, the study showed that both before and after OIT, all OIT-treated patients had more $IgG_4$ neutralizing antibodies than $IgG_4$ non-neutralizing antibodies. After OIT, $IgG_4$ neutralizing antibodies were higher only in persons with sustained OIT responses. In the mouse study, $IgG_4$ neutralizing antibodies inhibited IgE-mediated activation in response to an allergen challenge more than did non-neutralizing antibodies.

The study identified neutralizing $IgG_4$ antibodies to Ara h 2 as a potential biomarker of clinical efficacy of peanut OIT.

**COMMENT:** Only a minority of patients undergoing peanut OIT achieve tolerance, and currently no biomarker exists to identify these patients. This study identifies a subset of allergen-specific $IgG_4$ neutralizing antibodies against Ara h 2 epitopes that is associated with tolerance after discontinuation of OIT. This finding could lead to a future diagnostic test guiding the dosing, duration, and eventual discontinuation of peanut OIT once evidence of tolerance is achieved.

G.B.L.

Keswani T, LaHood NA, Marini-Rapoport O, et al. Neutralizing $IgG_4$ antibodies are a biomarker of sustained efficacy after peanut oral immunotherapy. J Allergy Clin Immunol. 2024;153(6):1611-1620.

Keywords: allergens, IgE, IgG, peanut hypersensitivity

## The Microbiome in Food Allergy: Consider Starting Treatment Early

Dysbiosis of the gut microbiota has been linked to the development of food allergy. Dysbiosis can cause shifts in alpha diversity, a measure of the number of taxa, and in beta diversity, a measure of similarity between samples. Data are lacking in children on the presence of specific beneficial or harmful microbiota in relation to the development of food allergy. To address this research gap, this real-world study characterized the gut microbiome of children aged 3 to 18 years with food allergy.

Children with allergy to cow's milk, hen's egg, and peanut and healthy control participants were recruited prospectively. After enrollment, children with food allergy were further grouped into those with persistent or resolving food allergy. Alpha and beta diversity were compared between children with and without food allergy. The authors reviewed the literature to choose a priori taxa for • • •

comparison of differential abundance.

The demographic characteristics of the 56 children with food allergy did not differ from those of the 14 healthy control children. Older children with peanut allergy had lower alpha diversity than healthy control children, whereas alpha diversity did not differ in children under the age of 3. Beta diversity differed by age. Eleven a priori taxa were differentially abundant regardless of age or type of food allergy. Older children with peanut, milk, or egg allergy had lower differential abundance of several taxa, and children with peanut allergy were less likely to have *Coprococcus* taxa. *Coprobacillus* and *Clostridium_sensu_stricto* genera were slightly less abundant in children with persistent food allergy than in those with resolving food allergy.

The study concludes that children with food allergy have evidence of dysbiosis, which is more prominent in children older than 3 years.

**COMMENT:** This article contributes to our understanding of the role of the microbiome in food allergy. Younger children, with and without food allergy, have fewer differences in gut microbiota. Children older than 3 years have dysbiosis that associates with food allergy, especially peanut allergy. This dysbiosis can lead to changes in both adaptive and innate immune responses. The authors remind us to consider starting interventions or treatment for food allergy below the age of 3 years.

V.H.T.

Ponda P, Cerise JE, Navetta-Modrov B, et al. The age-specific microbiome of children with milk, egg, and peanut allergy.
Ann Allergy Asthma Immunol. 2024;133(2):203-210.

Keywords: allergens, food allergy, gastrointestinal microbiome

## Disparities Continue in Patients With Atopic Dermatitis and Food Allergy

Previous research has shown that Black and Hispanic children are twice as likely as White children to visit the emergency department for food allergy (FA) and are disproportionately affected by atopic dermatitis (AD), a risk factor for FA. These authors further explored how race, ethnicity, and socioeconomic status affect the diagnosis of FA in children with AD.

The authors reviewed the electronic medical records of children with a physician diagnosis of AD. Rather than use ZIP codes, the authors matched the children's addresses to their census block to calculate the area deprivation index (ADI). Higher ADI values indicate greater socioeconomic disadvantage.

Of 3365 children, 41% were non-Hispanic Black, 34% were Hispanic, 7% were Asian, and 15% were non-Hispanic White. About 60% of the study sample had Medicaid insurance, which was more common among Black and Hispanic children. Black and Hispanic children tended to live in neighborhoods with a higher ADI. In logistic regression analyses, Black and Asian children were more likely than White children to have an FA diagnosis. The mean ADI was lower in children with an FA diagnosis but was not associated with being evaluated by an allergy/immunology specialist. However, among children with a diagnosed FA, Hispanic and Black children were less likely to have been evaluated by an allergist and to have undergone both skin and blood testing.

This real-world study found that Black and Hispanic children were less likely to have seen an allergist, although many did have referrals in place. The study findings provide further evidence of racial/ethnic and socioeconomic disparities in FA diagnosis.

**COMMENT:** In this important study, disappointingly, but not surprisingly, Hispanic and non-Hispanic Black children with AD and diagnosed FA were significantly less likely to have been evaluated by an allergist, and non-Hispanic Black children were more likely to have undergone no objective FA testing, than White children. These disparities lead to labeling that is inaccurate, affects nutrition, and decreases quality of life. This is another call to action. If we are not aware of our biases, we will not be able to address the disparities and will only continue to contribute to inequity in our care of different patient populations.

V.H.T.

Stephen ED, Wang S, Shah M, et al. Sociodemographic factors linked to food allergy diagnosis among high-risk children with atopic dermatitis.
Ann Allergy Asthma Immunol 2024:133:86-92.

Keywords: atopic dermatitis, food allergy, health care disparities

## Losartan Investigated in Treatment of Eosinophilic Esophagitis

Transforming growth factor (TGF)-β1 is elevated in eosinophilic esophagitis (EoE) and leads to esophageal dysmotility and the expression of genes that drive fibrosis. Losartan is an angiotensin II type 1 receptor antagonist that reduces TGF-β1 activity. This open-label pilot study investigated the effects of losartan on endoscopic features, esophageal histopathology, symptom scores, and quality of life in patients with EoE.

Fifteen pediatric and adult patients (age range, 5-23 years) were enrolled. Participants were treated with an initial 4-week course of 0.7 to 0.9 mg/kg losartan per day, followed by a 12-week maintenance course with up-titration to 1 to 1.4 mg/kg per day. Seven of the 15 patients had connective tissue disorder (CTD).

After 16 weeks, the peak eosinophil count was not reduced significantly in the proximal or distal esophagus in the total study group, although 4 patients did achieve remission according to peak eosinophil count. Reductions

in proximal and distal EoE Histology Scoring System (EoEHSS) scores were not significant, although some patients showed a trend toward improvement on individual domains of the score. Although there was a trend toward improvement in the proximal esophagus, EoE Endoscopic Reference Scores did not significantly improve with losartan treatment. Patient-reported outcomes as measured with the Pediatric EoE Symptom Score and Pediatric Quality of Life Inventory EoE Module improved with losartan. The authors also analyzed gene expression after losartan treatment and found that 29 genes that are dysregulated in EoE were differentially expressed compared with baseline values and those in the control group. Esophageal TGF-β expression was reduced with losartan.

The study findings suggest that losartan may be effective in a subset of patients with EoE. Study limitations include the small sample size and pediatric focus.

**COMMENT:** TGF-β1 has a critical role in immunoregulation, fibrosis, and remodeling. While this pilot study did not find a significant reduction of peak eosinophil counts, a subset of patients demonstrated improvement in histologic and endoscopic features. This research lays the groundwork for future study of losartan and other drugs that impact TGF signaling in patients with EoE.

S.W.S.

Abonia JP, Rudman Spergel AK, et al. Losartan treatment reduces esophageal eosinophilic inflammation in a subset of eosinophilic esophagitis. J Allergy Clin Immunol Pract. 2024;12(9):2427-2438.

Keywords: angiotensin II type 1 receptor blockers, eosinophilic esophagitis, losartan

## Mixed Results With Benralizumab for Eosinophilic Esophagitis

Benralizumab depletes eosinophils but its efficacy in treating patients with eosinophilic esophagitis (EoE), in which eosinophils accumulate in the esophagus, is unclear. This phase 3 trial studied the efficacy and safety of benralizumab on 2 outcomes in adults and adolescents with EoE: number of eosinophils per high-power field (HPF) and score on the Dysphagia Symptom Questionnaire (DSQ).

The trial was conducted at 78 sites in 12 countries. Eligible patients had at least 15 eosinophils/HPF at 2 or more levels of the esophagus. The trial protocol included a 24-week double-blind treatment period (benralizumab or placebo) and a 24-week open-label treatment period. Benralizumab was dosed as 30 mg subcutaneously every 4 weeks. Histologic response was defined as no more than 6 eosinophils/HPF.

A total of 211 patients were randomly assigned to benralizumab (n=104) or placebo (n=107). Study participants were majority White (93%) and male (75%). About 88% of patients in the benralizumab group had a histologic response at 24 weeks vs 7% of the placebo group. However, the change from baseline in the DSQ score did not differ significantly between the groups at 24 weeks. Findings at 52 weeks were similar. Blood eosinophils were depleted in the benralizumab group starting at week 8. The EoE Endoscopic Reference Score, which reflects endoscopic abnormalities, did not differ between the groups at week 24 or 52. Symptoms such as dysphagia, abdominal pain, and nausea did not differ between groups. Adverse events in both groups included COVID-19, headache, and nasopharyngitis.

Although benralizumab depleted tissue and blood eosinophils, the trial did not identify a subgroup of patients with improved dysphagia symptoms.

**COMMENT:** This study demonstrated that benralizumab significantly reduced the presence of tissue eosinophilia in adolescent and adult patients with EoE. However, endoscopic gross abnormalities and symptoms did not significantly change compared with placebo. Symptom improvement and endoscopic improvement are important for quality of life and reduction in fibrostenotic complications. These findings indicate that pathways other than tissue eosinophilia contribute to EoE inflammation.

S.M.K.

Rothenberg ME, Dellon ES, Collins MH, et al. Eosinophil depletion with benralizumab for eosinophilic esophagitis.
N Engl J Med. 2024;390(24):2252-2263.

Keywords: benralizumab, deglutition disorders, eosinophilic esophagitis

## Donidalorsen for Prophylactic Treatment of Hereditary Angioedema

Two recent publications in *New England Journal of Medicine* report the results of phase 3 trials of treatments for hereditary angioedema (HAE): donidalorsen as a prophylactic treatment and sebetralstat for on-demand treatment. In the first of these, the OASIS-HAE study investigators report on prophylactic treatment with donidalorsen, an investigational antisense oligonucleotide that binds to prekallikrein mRNA.

Donidalorsen was administered in doses of 80 mg subcutaneously every 4 weeks (n=45) or every 8 weeks (n=23) vs placebo (n=22) in patients at least 12 years old with confirmed HAE. The primary end point was the number of confirmed attacks. Five patients withdrew because of lack of efficacy (2 in the donidalorsen groups and 3 in the placebo group), 1 patient because of pregnancy, and 1 because of an adverse event. Most (93%) patients had type I HAE.

The time-normalized attack rate was 0.44 in the group receiving donidalorsen every 4 weeks, 1.02 in the 8-week group, and 2.26 in the placebo group. The median reduction in the attack rate was 90% in the 4-week group, 83% in the 8-week group, and 16% in the placebo group. Compared with the placebo group, the mean attack rate from

week 5 (4 weeks after the first dose) to week 25 was 87% lower in the 4-week group and 60% lower in the 8-week group. A majority (82%) of patients in the 4-week group experienced a greater than 70% reduction in the number of HAE attacks. Slightly more than half (53%) in the 4-week group had no attacks. In the 8-week group, 65% of patients had a reduction in attacks of 70% or more. Use of on-demand therapy was 92% lower in the 4-week group than in the placebo group. Quality of life scores improved significantly in the 4-week group. Most adverse events were mild or moderate in severity. The most common were erythema at the injection site, headache, and nasopharyngitis.

This phase 3 study showed that prophylactic treatment with donidalorsen reduced the rate of HAE attacks and, when administered every 4 weeks, improved patient-reported quality of life.

**COMMENT:** Donidalorsen significantly reduced HAE attacks at both the 4- and 8-week administration intervals compared with placebo. The low adverse effect profile, solid efficacy, and less frequent administration may improve the quality of life of patients with HAE.

S.M.K.

Riedl MA, Tachdjian R, Lumry WR, et al. Efficacy and safety of donidalorsen for hereditary angioedema.
N Engl J Med. 2024;391(1):21-31.

Keywords: antisense oligonucleotides, donidalorsen, hereditary angioedema

relief was reported after administration of 300 or 600 mg sebetralstat compared with placebo. Median time to symptom relief was 1.6 hours with the 300-mg dose and 1.8 hours with the 600-mg dose vs 6.7 hours for placebo. The median time to a reduction in severity was less than 12 hours for both sebetralstat doses, and close to 50% of attacks were completely resolved within 24 hours. Adverse events did not differ significantly among the 2 doses of sebetralstat and placebo.

Participants in this clinical trial reported experiencing more rapid symptom relief, more rapid reduction in symptom severity, and faster resolution of HAE attacks with on-demand sebetralstat than with placebo.

**COMMENT:** Oral sebetralstat demonstrated faster time to onset of symptom relief, to symptom resolution, and to decrease in attack severity compared with placebo. Of note, there were too few laryngeal attacks to determine a significance in reducing this specific attack type. Nonetheless, an on-demand treatment option that is portable and accessible may reduce the delays in treatment and complications from those delays.

S.M.K.

Riedl MA, Farkas H, Aygören-Pürsün E, et al. Oral sebetralstat for on-demand treatment of hereditary angioedema attacks.
N Engl J Med. 2024;391(1):32-43.

Keywords: hereditary angioedema, pyrazoles, sebetralstat

## Sebetralstat for On-Demand Treatment of Hereditary Angioedema

In the second of 2 recent publications in *New England Journal of Medicine* on hereditary angioedema (HAE) treatment, the KONFIDENT study investigators report on the use of oral sebetralstat for on-demand treatment. Treatment guidelines recommend that patients carry on-demand therapy, but the need to administer these medications parenterally reduces adherence. Sebetralstat is an orally administered kallikrein inhibitor.

Participants of this trial were at least 12 years of age and had a confirmed diagnosis of HAE. Participants were randomly assigned to administer 300 or 600 mg sebetralstat or placebo to themselves as early as possible after each eligible HAE attack in 1 of 6 sequences (eg, placebo for attack 1, 600 mg sebetralstat for attack 2, 300 mg sebetralstat for attack 3). HAE attacks were eligible for treatment if the participant could identify its start and at least 48 hours had elapsed since a previous attack. The primary end point was the time at which participants rated their symptoms as being "a little better" on the Patient Global Impression of Change scale.

A total of 110 participants administered sebetralstat or placebo for at least 1 attack. Participants administered a study agent in a median time of 41 minutes. Faster symptom

## First-Generation Antihistamines and Seizure Risk?

The first-generation H1 antihistamines developed in the 1940s and 1950s cross the blood–brain barrier and suppress histamine transmission in the central nervous system. A body of research in animals and adults suggests that these medications can also affect brain waves and induce seizures. Fewer data are available for children. Using a conditional logistic regression model, this study examined associations between use of first-generation antihistamines and seizures in children. The antihistamines studied were chlorpheniramine maleate, mequitazine, oxatomide, piprinhydrinate, and hydroxyzine hydrochloride.

The retrospective cohort study used deidentified data from the National Health Insurance Service database in Korea. Each participant in the case-crossover study design served as their own control. The data analyzed were for 11,729 children with a seizure event. The study sample included slightly more boys than girls. Children were divided into 3 age groups for analysis: 6 to 24 months of age, 25 months to 6 years, and 7 years and older. About one-third of the participants had a perinatal condition, the most common being congenital malformations. The adjusted odds ratio for risk of a seizure event within 15 days of antihistamine prescription was 1.22. In the analysis of participant char- • • •

acteristics, the authors found significant interaction effects according to the child's age at the index date (ie, the date on which a seizure event occurred). Seizure risk was higher in children aged 6 to 24 months.

This large study reported that prescription of a first-generation antihistamine increased risk for seizures by 22%, especially in children aged 6 to 24 months. The authors advise that the risks and benefits of prescribing H1 antihistamines to children be considered carefully.

**COMMENT:** First-generation antihistamines have fallen out of favor with allergists globally because of their known anticholinergic adverse effects and ability to cross the blood–brain barrier. While many limitations exist with the study, including the retrospective nature and possible omission of other confounding factors, the findings should lead to further discussion between providers and patients and their families on the risks and benefits of first-generation antihistamines in this age group. The findings should also further shift the practice of utilizing second-generation antihistamines when needed, which appear to have a lower association with seizures.

S.R.J.

Kim JH, Ha EK, Han B, et al. First-generation antihistamines and seizures in young children. JAMA Netw Open. 2024;7(8):e2429654.

Keywords: antihistamines, child, seizures

## Does Biologic Therapy Affect COVID Vaccine Immunity?

The biologic therapy dupilumab targets the interleukin (IL)-4 pathway, whereas IL-5 is targeted directly by mepolizumab and indirectly by benralizumab. Because IL-5 and IL-4 play roles in adaptive immunity, biologic therapies that inhibit these cytokines could affect immunity after SARS-CoV-2 vaccination. To study the possibility, these authors evaluated antibody and cellular immune responses up to 6 months after vaccination in patients receiving benralizumab, dupilumab, and mepolizumab.

The study group consisted of 57 patients being treated with a biologic therapy for severe asthma or atopic dermatitis. Control samples were from 46 immunologically healthy persons not being treated with a biologic. At 180 days after the second vaccination dose, combined IgG, IgM, and IgA antibody responses to the SARS-CoV-2 spike protein and receptor binding domain were significantly lower in the biologic-treated group than in the control group. The biologic group also had lower antibody binding to the receptor binding domain of the Delta and Omicron variants. The biologic group showed lower pseudovirus neutralization activity against SARS-CoV-2 and the Delta variant. In an experimental system using live virus neutralization, samples from the biologic group were less able to block live virus from infecting cells expressing angiotensin-converting enzyme 2 receptor. By analyzing subgroups of patients with and without asthma, the study showed that biologic therapy and not asthma was driving the lower pseudovirus neutralization activity. No significant differences were found between the 3 biologics.

This prospective observational study showed that patients treated with benralizumab, dupilumab, or mepolizumab have lower antibody levels after mRNA vaccination for SARS-CoV-2 compared with immunologically healthy persons not receiving a biologic therapy. Research is needed into better vaccine strategies for people being treated with anti–IL-4 and anti–IL-5 therapies.

**COMMENT:** Biologics that target type 2 cytokines have been associated with increased upper respiratory tract and herpesvirus infections. This study of COVID-19 vaccination in asthma and atopic dermatitis patients receiving benralizumab, mepolizumab, and dupilumab found that biologic use was associated with reduced vaccine antibody levels and decreased neutralizing ability. However, biologics such as dupilumab have previously been shown to reduce the risk of severe COVID-19, so despite the reduced antibody response, the anti-inflammatory effects of biologics may also provide a protective effect.

G.B.L.

Runnstrom MC, Lamothe PA, Faliti CE, et al. Patients taking benralizumab, dupilumab, or mepolizumab have lower postvaccination SARS-CoV-2 immunity. J Allergy Clin Immunol. 2024;154(2):435-446.

Keywords: antibodies, asthma, COVID-19 vaccines

## The Realities of Aeroallergen Polysensitization

Most patients with allergies are sensitized to several specific allergens, but not all hypersensitivities cause clinical symptoms. Information about a patient's sensitization profile can allow for personalized treatment. These authors studied specific IgE (sIgE) patterns toward aeroallergens in a German population using the ImmunoCAP IgE platform (Thermo Fisher Scientific).

In 500 patients with allergies, serum sIgE levels to 33 allergenic sources and 43 molecular allergens were analyzed and the relations between sensitization and symptoms were explored. The patients' mean age was 39 years, and 58% were women.

The article reports the percentages of patients sensitized to each allergenic source, ranging from 8% to the mold *Alternaria alternata* to 59% to *Betula verrucosa* (birch) pollen. A total of 81% of patients were sensitized to 2 or more allergens. More than 50% of patients had polysensitization profiles to airborne allergens. Sensitization to tree pollen was driven primarily by the molecular allergen Bet v 1 (84%). As the number of sensitizations increased, the proportion of patients with asthma also increased. Severe

rhinitis symptoms were associated with sensitization to more than 3 allergens. In an analysis of response to molecular allergens in patients with and without concomitant asthma, more patients sensitized to the mite allergen Der p 10 presented with concomitant asthma. Patients with rhinitis and asthma had greater sensitization to Der p 1 and the dog allergens Can f 1 and Can f 6 than patients with rhinitis only.

In this study population, more than 80% of patients with allergy were polysensitized, and polysensitization was associated with more severe symptoms and the presence of asthma.

**COMMENT:** Traditional teachings have suggested that US patients have a higher rate of polysensitization to aeroallergens compared with European populations. This German study shows the opposite with 81% of patients being polysensitized. One key concept this article explores is the idea of polysensitization versus polyallergy. While many patients may have positive testing results to various allergens, it is key to determine clinically relevant allergies through a detailed history and, in the future, molecular assays. This allows more targeted allergen immunotherapy, which can lead to improved efficacy long-term.

S.R.J.

Cacheiro-Llaguno C, Mösges R, Calzada D, et al. Polysensitisation is associated with more severe symptoms: the reality of patients with allergy. Clin Exp Allergy. 2024;54(8):607-620.

Keywords: allergens, hypersensitivity, immunoglobulin E

## Dupilumab Does Not Significantly Improve Chronic Urticaria In Omalizumab Nonresponders

Dupilumab blocks interleukin (IL)-4 receptor α and inhibits IL-4 and IL-13 signaling. Omalizumab is the only approved therapy for antihistamine-refractory chronic spontaneous urticaria (CSU), but case reports have shown improvement of CSU with dupilumab treatment. The 2 LIBERTY-CSU CUPID trials are phase 3 studies of dupilumab in patients with CSU with an inadequate response to prior therapy. Patients in study A were omalizumab naïve; those in study B were omalizumab intolerant or incomplete responders. Patients in both studies remained on their background dose of second-generation H1 antihistamines (H1-AH).

Half or more of patients in both studies were taking higher-than-approved doses of H1-AH, and nearly 70% of patients had severe disease activity at baseline. After 24 weeks of dupilumab treatment, omalizumab-naïve patients showed reduced urticaria activity, itch severity, and hives severity as assessed with the Urticaria Activity Score (UAS7), Itch Severity Score (ISS7), and Hives Severity Score (HSS7), respectively. Dupilumab improved overall disease control. In group B, the change in UAS7 at 24 weeks was significant and the change in HSS7 was nominally significant. Overall disease control trended toward improvement. Pooled data from both studies were used to analyze safety outcomes. The percentage of patients with any treatment-related adverse event was similar for dupilumab and placebo.

These trials are the first to assess dupilumab in patients who continue to experience symptoms despite standard-of-care treatment for CSU. The smaller treatment effect observed in patients who were omalizumab intolerant or incomplete responders may indicate that dupilumab has only minimal benefit in patients who do not respond to omalizumab.

**COMMENT:** Approximately 25% of patients with CSU have an incomplete response to omalizumab, and thus other advanced therapies are needed. This report from the LIBERTY-CSU CUPID trial found that dupilumab therapy in omalizumab nonresponders improved the UAS7 by a mean of 5.8, which did not achieve statistical significance and is below a minimum importance difference of approximately 9.5-10.5. Therefore, even if a larger sample size would allow dupilumab to achieve statistical significance, the lack of a clinically significant effect limits the utility of dupilumab among omalizumab nonresponders.

G.B.L.

Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): two randomized, double-blind, placebo-controlled, phase 3 trials.
J Allergy Clin Immunol. 2024;154(1):184-194.

Keywords: chronic urticaria, dupilumab, monoclonal antibodies, omalizumab

## Positive PEG Allergy Testing Doesn't Necessarily Mean Avoiding All PEG-Containing Medications

Polyethylene glycols (PEGs) are additives found in medications, cosmetics, and food that can cause immune-mediated reactions including anaphylaxis. This retrospective study analyzed the medical records of patients with suspected immediate PEG hypersensitivity at 4 medical centers in the United Kingdom over a 7-year period. Patients underwent skin-prick testing, intradermal testing when applicable, and drug provocation testing when the results of the other tests were negative.

The 44 patients studied ranged in age from 18 to 72 years; women outnumbered men 2.7 to 1. A total of 70 index drugs were identified. Macrogol laxatives were the most common (23%), followed by depo-medroxyprogesterone (19%), oral penicillin V (10%), and depo-methylprednisolone (10%). PEG allergy was confirmed in 42 patients, and more than half of these patients experienced Brown's grade III anaphylaxis. Of the 42 PEG-allergic patients, 24 were diagnosed via positive skin-prick testing, 15 by positive intradermal testing, and 3 by positive drug provocation testing. Five patients experienced systemic reactions during intradermal testing. Hypersensitivity tended to occur with drugs containing PEG molecular weights of 3350 and • • •

above. Nine of the patients with PEG allergy tolerated 5 different drugs containing PEG. COVID-19 vaccination status was known for 21 patients, 16 of whom had been vaccinated and tolerated the vaccine.

The authors conclude that PEG allergy affects more women than men and occurs at younger ages than other drug hypersensitivities. More research is needed to understand PEG thresholds and equivalent doses of different administration routes.

**COMMENT:** This study provides evidence against the misconception that PEG allergy is associated with "reacting to everything." In this study, implicated drugs contained larger amounts of PEG, and positive PEG testing occurred more often with higher molecular weight PEGs of 3350 or more. Multiple patients with positive PEG testing tolerated PEG-containing medications (n=9) and PEG-containing vaccines (n=5). This suggests that even patients with positive PEG testing results may be able to tolerate certain PEG-containing drugs, particularly if the PEG is included in lower quantities than in the culprit drug and is of lower molecular weight than the culprit PEG.

I.M.O.

Kayode OS, Nakonechna A, Siew LQC, et al. Polyethylene glycol hypersensitivity, patient outcomes in a 7-year retrospective study. Ann Allergy Asthma Immunol. 2024;133(1):93-100.

Keywords: anaphylaxis, COVID-19 vaccines, polyethylene glycol

## Epinephrine Auto-Injectors: Where's the Medication Going?

Epinephrine autoinjector (EAI) devices are used for the first-line treatment of anaphylaxis. The fastest peak epinephrine concentrations occur after intramuscular injection in the midthigh, but the device needles may not reach the intramuscular depth in all users. There is also a small risk of injection in the bone. To estimate percentages of subcutaneous and intraosseous injection, this study compared the needle lengths of 4 devices approved in the European Union (EpiPen [Mylan], Anapen [BioProject], Jext [ALK], and Emerade [Medeca]) with ultrasound-measured skin-to-muscle and skin-to-bone depth.

The prospective study had a convenience sample of 68 patients with diagnosed allergy who underwent ultrasound imaging. The patients' mean age was 50 years, and 54% were male. Eighteen percent had obesity. The Anapen device, which had the shortest needle length, had the highest estimated frequency of subcutaneous injection of 65%-66%. The EpiPen and Jext devices had similar needle lengths and had estimated rates of subcutaneous injection ranging from 29% with maximal compression of the ultrasound probe to 38% without compression. The Emerade device had the longest needle and had the lowest estimated rate of subcutaneous injection but a small 4% risk for intraosseous injection. Female sex predicted subcutaneous injection for all devices. Obesity-related variables including body mass index, abdominal circumference, and skinfold thickness did not predict subcutaneous injection.

Estimated rates of subcutaneous injection varied by device, and women were predicted to be 1.3- to 2.0-fold more likely to experience subcutaneous injection.

**COMMENT:** There is the potential for differences in EAI efficacy between men and women regardless of body habitus because of a higher likelihood for subcutaneous administration in women. The findings of this study suggest that sex-specific EAI injection guidelines are likely needed since the projected frequency of subcutaneous administration was 65% in women and 0% in men for the Epi-pen EAI. Injecting with maximal compression decreased the chance for subcutaneous administration, highlighting the importance of patient education when prescribing EAIs. Potential risk for intraosseous administration was fortunately not observed with the most commonly used EAI, Epi-pen.

I.M.O.

Lefevre S, Goetz C, Hennequin L, et al. Frequencies and predictors of subcutaneous and intraosseous injection with 4 epinephrine autoinjector devices. Ann Allergy Asthma Immunol. 2024;133(2):194-202.

Keywords: anaphylaxis, epinephrine

## Reflexive IgG Testing Not Always Needed for IgE Deficiency

About 3% of the population has IgE deficiency defined as concentrations less than 2 IU/mL. However, the clinical significance of low IgE is unclear, as is whether IgE deficiency is associated with hypogammaglobulinemia. This letter reports a study aiming to avoid the confounding biases of past studies of patients with medical indications for IgE testing by measuring values in a healthy cohort of military recruits.

In a sample of 3000 recruits, the authors identified persons with IgE deficiency and a group of sex-matched control subjects with IgE greater than 10 IU/mL. The study cohort was 18% female with a median age of 19 years. Two percent had IgE deficiency. Whereas IgG was lower at baseline in the group with IgE deficiency, IgG did not differ significantly between the groups 18 months later. One person in the IgE deficiency group had hypogammaglobulinemia compared with no one in the control group. The difference in incidence of hypogammaglobulinemia between the groups with and without IgE deficiency was not significant.

The authors conclude that reflex testing of IgG in young, healthy individuals with IgE deficiency "is unlikely to identify hypogammaglobulinemia." Reflex testing may be appropriate in patients with other clinical indications such as a history of immunodeficiency, chronic sinonasal or lower respiratory tract symptoms, or malignancy.

**COMMENT:** IgE less than 2 IU/mL may help to dis-

tinguish primary versus secondary antibody deficiency and it has been suggested that IgG levels be reflexively tested after detection of IgE deficiency. By comparing IgG levels among healthy military recruits with or without IgE less than 2 IU/mL, the authors were able to show that while IgG levels may be lower in people with IgE deficiency, IgG levels are still in the normal range. Reflexive IgG testing in healthy individuals is unlikely to identify clinically significant hypogammaglobulinemia. IgG level checks should continue to be prompted primarily by clinical histories that raise suspicion for primary antibody deficiency.

I.M.O.

Makin T, Borish L, Nylund CM, et al. IgE deficiency is not associated with hypogammaglobulinemia in a large cohort of military recruits.
Ann Allergy Asthma Immunol. 2024;133(2):220-222.

Keywords: IgE, hypogammaglobulinemia

## Developing Machine Learning Methods for Pollen Forecasting

Pollen affects the quality of life of people with allergies and pollen-induced asthma, and high pollen concentrations have been associated with cardiovascular disease. Pollen forecasts could help pollen-sensitive individuals avoid exposure to high pollen concentrations. These authors used different computational intelligence methods to develop forecasting tools and to evaluate variables affecting future pollen concentrations.

The input data included pollen concentrations from 23 cities worldwide and 22 environmental variables. Two types of computational models were compared—gradient boosting using an algorithm called CatBoost and deep learning—for their ability to predict daily total pollen concentrations up to 14 days in advance.

The 5 most important environmental variables affecting the forecast of daily total pollen concentrations were the past daily pollen concentration, future temperature at 2 m above surface level, past temperature at 2 m above surface level, past soil temperature at a depth of 28 to 100 cm, and past soil temperature at a depth of 0 to 7 cm. The CatBoost model performed better when forecasting in the short term (up to 6 days), and the deep learning model performed better for forecasting from day 7 on. The models performed differently in different cities. The models made the best forecasts for Santiago, Geneva, Mexico City, and Tulsa.

Innovative aspects of the study include the use of 2 up-to-date artificial intelligence models to forecast pollen concentrations 2 weeks in advance and the incorporation of data from all 5 continents.

**COMMENT:** These researchers used machine learning methods to forecast pollen concentrations for a 14-day interval and predict total daily pollen concentrations for various stations around the world. With further study and refinement, these tools may provide valuable guidance for clinicians and allergy sufferers alike.

S.W.S.

Makra L, Coviello L, Gobbi A, et al. Forecasting daily total pollen concentrations on a global scale. Allergy. 2024;79(8):2173-2185.

Keywords: allergens, pollen, forecasting methods

## REVIEWS OF NOTE

**COMMENT:** RSV infection poses a major risk for older adults, particularly those with underlying conditions such as chronic obstructive pulmonary disease, heart failure, and immunodeficiency. This review of the current epidemiologic, diagnostic, and management landscape is informative and timely as we approach a new RSV season—our second with licensed vaccines.

S.W.S.

Wildenbeest JG, Lowe DM, Standing JF, et al. Respiratory syncytial virus infections in adults: a narrative review.
Lancet Respir Med. 2024;12(10):822-836.

**COMMENT:** This review discusses several considerations regarding the implementation of omalizumab in the treatment of food allergy, including dosing, assessing treatment response, application to adult patients, safety, and the role of concomitant oral immunotherapy.

G.B.L.

Casale TB, Fiocchi A, Greenhawt M. A practical guide for implementing omalizumab therapy for food allergy.
J Allergy Clin Immunol. 2024;153(6):1510-1517.

**COMMENT:** This review provides a concise summary of the diagnostic criteria, workup, differential diagnosis, and treatment of patients with mast cell activation syndrome.

G.B.L.

Castells M, Giannetti MP, Hamilton MJ, et al. Mast cell activation syndrome: current understanding and research needs.
J Allergy Clin Immunol. 2024;154(2):255-263.