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

American College of Allergy, Asthma & Immunology

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A Mechanical Model of Asthma-Induced Airway Inflammation

Despite the availability of therapies to relieve airway constriction or type 2 airway inflammation, many patients with asthma continue to experience airway hyperresponsiveness. This group is studying a process called *cell extrusion*, in which cells are triggered to extrude from the airway epithelial layer to make room for newly dividing cells to maintain cell number homeostasis. Here the authors used a mouse model to study whether bronchoconstriction triggers excess airway epithelial extrusion.

In lung slices treated with methacholine and primed with egg or house dust mite (HDM) allergen, the authors observed bronchoconstriction, severe airway epithelial crowding, and excess epithelial cell extrusion. Although albuterol treatment relaxed the constricted airways, it did not prevent epithelial extrusion. When the authors added an inhibitor of extrusion, they found that extrusions after methacholine treatment were decreased, and the inhibitor's ability to block extrusion was not impaired by albuterol treatment. The extrusion inhibitor also reduced mucus secretion in primary airways. The finding of increased cell extrusion after bronchoconstriction was confirmed in human lung biopsy samples from patients with moderate or severe asthma.

In a live mouse model, the investigators treated HDM-primed mice with both albuterol and inhibitors of extrusion. The addition of the inhibitor led to preserved airway epithelia after methacholine challenge, similar to that in unchallenged mice.

The study results suggest that the inflammation that follows an asthma attack could be prevented by eliminating the bronchoconstriction-induced epithelial extrusion. The safety of the extrusion inhibitor studied remains to be tested in humans. • • •

FEATURE ARTICLES

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The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

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

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COMMENT: Bronchoconstriction and airway hyperresponsiveness are often framed as consequences of airway inflammation in asthma. This study introduces the concept of the "mechano-inflammatory vicious cycle," where epithelial cell extrusion induced by bronchoconstriction exacerbates inflammation that leads to further bronchoconstriction and injury. Inhibitors of cellular extrusion appear to improve airway inflammation, revealing a potential future therapeutic target in asthma.

G.B.L.

Bagley DC, Russell T, Ortiz-Zapater E, et al. Bronchoconstriction damages airway epithelia by crowding-induced excess cell extrusion.
Science. 2024;384:66-73.

Keywords: airway constriction, asthma

Achieving Remission With Biologics for Asthma

Given the availability of novel biologic therapies for severe asthma, this study examined how many treated patients achieve clinical remission and the predictors of response. Data were from the Danish Severe Asthma Register. *Clinical response* was defined as a reduction in the annualized exacerbation rate of at least 50% in patients with at least 2 exacerbations in the previous year and a reduction in dose of oral corticosteroids (OCS) from baseline of at least 50%. *Clinical remission* was defined as a complete absence of exacerbations, with no need for maintenance OCS, and a score on the 6-question Asthma Control Questionnaire of 1.5 or lower after 12 months of treatment.

Of 501 patients, 397 (79%) achieved clinical response, and of those, 97 (24%) achieved clinical remission (19% of the total study population). Patients who achieved clinical response were less likely to have used maintenance OCS at baseline. Patients who achieved remission were more likely than those who achieved clinical response to be male, have a lower body mass index (BMI), to have higher FEV_1, and to have a higher blood eosinophil count. In the multivariate model, the strongest predictors of remission were BMI and duration of disease.

The authors conclude that although further studies are required, clinical remission appears to be an achievable treatment goal.

COMMENT: Biologics have revolutionized asthma management over the past 2 decades; however, they have limitations. This excellent cohort study out of Denmark showed that among patients with severe asthma, more had no response to biologic therapy (21%) than achieved remission (19%). Patients who achieved remission had a lower BMI, which suggests that weight loss should remain a pillar of long-term asthma care, although additional prospective studies are needed to confirm this finding. As allergists, we have traditionally evaluated and managed asthma as a complex, multifaceted condition, and we must continue this approach. Biologics should be used as a component of a comprehensive asthma management plan for patients with severe, uncontrolled asthma, but exercise, weight loss, allergen mitigation, and other pharmacotherapies remain essential to achieve optimum control.

S.R.J.

Hansen S, Baastrup Søndergaard M, von Bülow A, et al. Clinical response

and remission in patients with severe asthma treated with biologic therapies. Chest. 2024;165:253-266.

Keywords: asthma (severe), biologic therapies, clinical remission

17q21 Variants and Mucosal Host Defense in Child Asthma

Genetic variations at the 17q21 locus are associated with risk for childhood-onset asthma. One gene encoded by 17q21 is *GSDMB* (gasdermin B). These authors used genome-wide transcriptome analysis of nasal brush samples to explore 17q21 genotype–phenotype interactions in children.

The 261 children studied were part of the pediatric arm of the ALLIANCE (All Age Asthma) cohort of the German Center for Lung Research: 79 had "preschool wheeze," defined as at least 2 parent reports of recurrent wheezing; 104 had physician-diagnosed asthma; and 78 were healthy control children.

The study children were first stratified according to 17q21 genotyping of the single nucleotide polymorphism (SNP) *rs72163891* (ie, wild-type, heterozygous, homozygous). In children with preschool wheeze, there were strong differences in gene expression between those with the wild-type genotype and those with the mutant genotype (hetero- or homozygous). Gene expression analysis showed upregulation of *GSDMB* in homozygous wheezing and asthmatic children. Further analysis showed that *GSDMB* was the only gene on the 17q21 locus that was differentially expressed in children with wheeze and asthma. Increased *GSDMB* expression correlated with activation of a type 1 proinflammatory, cell-lytic immune, and natural killer signature. Conversely, type 1 and type 3 interferon expression were reduced in wheezing children.

The authors conclude that their findings may explain the increased susceptibility to respiratory viral infections in children with preschool wheeze who carry the 17q21 risk allele.

COMMENT: We continue to uncover layers of the complex interaction between genetic predisposition and environmental factors in the development of asthma. Investigating the cellular mechanisms by which the well-defined 17q21 genetic risk factor results in rhinovirus-induced wheezing in preschool children, the authors identify that expression of *GSDMB* in upper airway mucosa is a primary genetic driver of this particular phenotype and leads to a reduction in type 1 and type 3 interferon expression. We have known for some time that impaired antiviral responses exist in asthma and can sometimes be modulated with anti-IgE therapy. This study is an important step in understanding the mechanism by which a genetic risk factor could contribute to these observations.

T.G.C.

Jakwerth CA, Weckmann M, Illi S, et al. 17q21 variants disturb mucosal host defense in childhood asthma. Am J Respir Crit Care Med. 2024;209:947-959.

Keywords: asthma (child), genetics

Further Effects of Dupilumab on Lung Function in Children

Dupilumab blocks the receptor for IL-4 and IL-13, which are key drivers of type 2 inflammation. Previously reported results of the phase 3 LIBERTY ASTHMA VOYAGE study (NCT02948959) showed that dupilumab reduces exacerbations and improves FEV_1 in children aged 6 to 11 with uncontrolled moderate-to-severe asthma. This article reports further in-depth assessment of lung function in children randomly assigned to add-on dupilumab 100/200 mg by body weight or placebo every 2 weeks for 52 weeks. Results included the following:

- Dupilumab improved prebronchodilator percent-predicted (pp) FEV_1 and FEV_1 at 52 weeks, and the differences between the treatment and placebo groups were noticeable as soon as 2 weeks.
- Dupilumab improved postbronchodilator FEV_1 and $ppFEV_1$ at week 52.
- The difference between post- and prebronchodilator FEV_1 and between post- and prebronchodilator $ppFEV_1$ (ie, the bronchodilator response) was greater in dupilumab-treated patients.
- Dupilumab improved prebronchodilator forced vital capacity (FVC) and ppFVC.
- Dupilumab improved the pre- and postbronchodilator FEV_1/FVC ratio. Differences in the prebronchodilator ratio in children with type 2 asthma were evident as early as 2 weeks.
- The number needed to treat with dupilumab for 1 year to reverse airflow obstruction in 1 patient was 6 patients.

Dupilumab led to sustained improvement in various measures of lung function in children with moderate-to-severe asthma.

COMMENT: This study confirms rapid and sustained improvement in FEV_1, as well as in many other lung function parameters, in pediatric patients treated with dupilumab for persistent asthma. It is essential to improve and maintain lung function to reduce risk for fixed airway obstruction later in life, as well as to reduce exacerbations and systemic corticosteroid use given long-term effects on growth, adrenal function, and bone health. This information may guide clinicians in prescribing an asthma biologic depending on patient characteristics, lung function, exacerbation risk, and shared decision-making.

S.M.K.

Bacharier LB, Guilbert TW, Katelaris CH, et al. Dupilumab improves lung function parameters in pediatric type 2 asthma: VOYAGE Study. J Allergy Clin Immunol Pract. 2024;12:948-959.

Keywords: asthma (child), dupilumab

Effects of Inhaled Corticosteroids on Airway Gene Expression

Gene expression profiling has shown that airway gene expression differs in people with mild, moderate, and severe asthma, but these data are confounded by the effects of inhaled corticosteroids (ICS). To study the effects of ICS on gene expression in the absence of disease, these authors performed a bronchoscopy study in healthy adults.

The participants underwent 4 weeks of treatment with fluticasone propionate or observation only and underwent bronchoscopy at baseline and at the end of the study. Gene expression did not change significantly in the observation group. In the ICS-treated group, genes involved in steroid metabolism, cell proliferation, cell metabolism, and cytoskeletal changes were upregulated. In this sample of healthy adults, ICS did not upregulate the IL-17-dependent gene signature that is present in about one-quarter of people with severe asthma.

The genes most significantly downregulated were involved in type 2 inflammation and T cell–mediated adaptive immunity. Other downregulated genes were involved in innate or adaptive immunity and B cell function. The most downregulated gene was *FCER1A*, which encodes the α chain of the high-affinity IgE receptor. The pathway analysis showed downregulation of pathways related to innate and adaptive immunity and T cell receptor signaling. The study found minimal effects on the airway microbiome or DNA methylation.

The study findings identify genes for which expression is altered by ICS treatment independent of the effect of asthma.

COMMENT: By examining the effects of high-dose ICS on healthy airways, this study revealed information about baseline immune signaling and helps us decipher which pattern of gene expression is a feature of the disease rather than of treatment. This valuable knowledge can be applied to severe asthma management.

S.W.S.

Marchi E, Hinks TSC, Richardson M, et al. The effects of inhaled corticosteroids on healthy airways. Allergy. 2024 Apr 30.

Keywords: asthma, epigenetics

Experimental Evidence That Microplastics Harm Developing Airways

Microplastics are a significant contributor to worldwide plastic pollution. Indoor air contains microplastics shed from synthetic textiles, and several studies have identified microplastic fibers in lung tissues. This study sought to explore how long-term microplastic exposure affects the growth and differentiation of lung epithelial cells. The authors studied nylon and polyester microfibers and components that leached from nylon. The experimental models included organoid cultures prepared from human and mouse lung tissue, experimental animals, and air–liquid interface cultures.

The study found that nylon microfibers inhibited the growth of mouse and human lung organoids. In the human lung organoids, nylon fibers had a greater effect than polyester fibers. Components that leach from nylon inhibited airway epithelial growth. Nylon fibers affected organoid cultures during the differentiation phase (days 7–14 of culture) but not during the established phase (cultures >14 days old). RNA sequencing analysis showed that *Hoxa5* was upregulated after exposure to nylon fibers, which was confirmed by increased protein expression of Hoxa5 in nylon-exposed organoids.

Microplastics impair the differentiation of lung epithelial cells, and nylon fibers are more harmful than polyester. The mechanism of the effect of nylon may be via upregulation of *Hoxa5*.

COMMENT: Using a series of in vitro and in vivo experiments, the authors demonstrate that inhalable nylon exposure led to impaired differentiation of lung epithelial cells through the upregulation of *Hoxa5* but did not appear to affect already differentiated epithelial cells. This suggests, as with many environmental exposures, that some populations may be at higher risk for adverse pulmonary outcomes than others, such as children or people with underlying lung disease where there are higher rates of epithelial repair. Given how prevalent textile microplastics are, the horse may be out of the barn for exposure primary prevention. However, this study contributes to our understanding of how microplastics impact lung health, which will be important when considering secondary and tertiary prevention efforts.

T.G.C.

Song S, van Dijk F, Vasse GF, et al. Inhalable textile microplastic fibers impair airway epithelial differentiation.
Am J Respir Crit Care Med. 2024;209:427-443.

Keywords: lung epithelial repair, microplastics, nylon, polyester

Biologic Treatments for Severe Eosinophilic Asthma

The PRISM (Precision Medicine Intervention in Severe Asthma) study is an ongoing observational cohort study of Korean adults with severe asthma. This publication uses PRISM data to make head-to-head comparisons of the efficacy of mepolizumab, reslizumab, and dupilumab, prescribed according to Global Initiative for Asthma (GINA) treatment guidelines for at least 6 months, in patients with severe eosinophilic asthma.

Of the 141 patients analyzed, 50% received dupilumab, 28% received reslizumab, and 21% received mepolizumab. At least 1 exacerbation was experienced by 28%, 38%, and 43% of patients in the reslizumab, dupilumab, and mepolizumab groups, respectively, with no significant difference between groups. Lung function improved in all treatment groups, with no significant differences in baseline or slope of change of FEV_1 and asthma control test scores.

This analysis showed mepolizumab, reslizumab, and dupilumab to be comparable in terms of effects on exacerbations, lung function, and asthma control.

COMMENT: There are now more treatment options for asthma patients owing to an increasing number of approved asthma biologics. However, increasing options can pose a challenge in terms of selecting the optimal biologic. This study is the first to directly compare the efficacy of dupilumab, reslizumab, and mepolizumab using a standard protocol in patients with severe eosinophilic asthma. Other biologics were not included in the analysis because of small sample sizes, and this remains an area for future study. The 3 biologics studied appeared to have similar efficacy in improving asthma outcomes, suggesting that treatment decisions be guided by shared decision-making and other considerations such as concurrent atopic conditions.

I.M.O.

Pham DD, Lee JH, Kwon HS, et al. Prospective direct comparison of biologic treatments for severe eosinophilic asthma: findings from the PRISM study. Ann Allergy Asthma Immunol. 2024;132:457-462.

Keywords: asthma, epidemiology, prevalence

State-Level Variation in Severe Asthma Prevalence

Patients with severe asthma, who experience recurrent exacerbations and need multiple daily medications, have a disproportionately high health care burden. Analyzing geographic variations in severe asthma can help to uncover disparities in disease burden, but state-level data are lacking. To address this gap, this study analyzed data from 2 pharmacy databases.

The retrospective cohort study identified more than 2 million patients with asthma, 24% of whom had severe persistent disease. The patients' mean age was 51 years; 68% were female. The percentage of patients with severe asthma varied by state, ranging from 20% to 32%. Disease control also varied by state. Nationally, about 41% of patients with severe asthma experienced exacerbations, compared with about 45% of patients in Louisiana, Oklahoma, and Texas. The percentage of patients with exacerbations who visited the emergency department (14% nationally) was highest in Nevada (18%) and lowest in North Carolina (7%). Nationally, about 15% of patients used biologics compared with 10% of patients in Ohio, 6% of patients in New Mexico, and 2% of patients in Hawaii. Use of systemic corticosteroids varied from 49% in Alaska to 72% in Mississippi.

The study findings show that asthma disease burden is not distributed equitably across states. An interactive, web-based tool is available for health care providers to visualize geographic variations in severe uncontrolled asthma (https://us.epicentralmed.com/resources/asthma-heatmap-tool).

COMMENT: Asthma remains a significant health burden in the United States. This study identified even higher nationwide percentages of severe persistent asthma than the rate reported by the Global Initiative for Asthma (GINA). Importantly, this study is also the first to look at and find state-level geographic differences in percentages of severe persistent asthma, disease control, and use of biologics and systemic corticosteroids. These geographic differences are likely multifactorial, and further investigation into the factors influencing asthma severity, control, and treatment can further our understanding of this condition.

I.M.O.

Camargo CA Jr, Rane PB, Beck AF, et al. Geographic variation in disease burden among patients with severe persistent asthma in the United States. Ann Allergy Asthma Immunol. 2024;132:602-609.

Keywords: asthma, epidemiology, prevalence

Best Step-Up Treatments for Children With Uncontrolled Asthma

About 10% to 15% of children treated with low-dose inhaled corticosteroids (ICS) for asthma do not achieve good disease control. This review aimed to determine the best treatment options for children with uncontrolled asthma despite use of ICS. The review analyzed individual participant data and aggregate data from randomized controlled trials (RCTs). The primary outcomes assessed were exacerbations and asthma control. Of 144 trials eligible for study inclusion, individual participant data were available for 29 studies and aggregate data were extracted for 19. The network meta-analysis examined the evidence for ICS stratified by dose when combined with a long-acting β_2-agonist (LABA).

- For exacerbations, the best-ranked evidence was for medium-dose ICS plus LABA. Leukotriene receptor antagonist (LTRA) and placebo were least preferred.
- For FEV_1, rank probability plots suggested medium-dose ICS plus LABA as the best treatment.

The data contained too much uncertainty to make firm conclusions about preferred treatment for asthma control. The authors report that this is the first network meta-analysis to examine this research question in children and adolescents using individual participant data, although these data could not be retrieved from 96 potentially eligible trials.

COMMENT: On the basis of this network meta-analysis of 48 RCTs including over 8000 children with uncon- • • •

trolled asthma on ICS alone, the authors suggest that medium-dose ICS plus LABA should be considered as a preferential step-up treatment compared with medium-dose ICS for patients whose asthma remains uncontrolled with low-dose ICS. Potential biases exist as both the meta-analysis and numerous studies included in it were primarily industry sponsored. It's somewhat strange that there was no significant difference between low-dose ICS and high-dose ICS plus LABA regarding exacerbations, as one would have expected a similar treatment class effect as observed with medium-dose ICS plus LABA. This makes me wonder if the studies included in the meta-analysis were fundamentally limited by heterogeneous populations, which given the broad inclusion criteria for studies is certainly possible. Readers should also note that SMART (single maintenance and reliever therapy) was not evaluated here.

T.G.C.

Cividini S, Sinha I, Donegan S, et al. Best step-up treatments for children with uncontrolled asthma: a systematic review and network meta-analysis of individual participant data.
Eur Respir J. 2023;62:2301011.

Keywords: asthma (child), inhaled corticosteroids, long-acting beta-2 agonist

Does SARS-CoV-2 Infection Increase Risk for Asthma in Children?

Previous studies have established that rhinovirus and respiratory syncytial virus (RSV) infections increase risk for pediatric asthma. Less is known about whether SARS-CoV-2 infection contributes to asthma risk. In a retrospective cohort study, these authors examined risk for new asthma diagnosis in 27,423 children aged 1 to 16 years who underwent PCR testing for SARS-CoV-2 in March 2020 through February 2021.

Data were extracted from electronic health records in the Children's Hospital of Philadelphia Care Network. The authors used multivariable Cox regression models to study risk of a new asthma diagnosis according to SARS-CoV-2 positivity.

SARS-CoV-2-positive children (11.5% of the cohort) were more likely than children who tested negative (88.5%) to be older, to be Black, to be insured by Medicaid, to have a higher body mass index (BMI), and to have allergic rhinitis. In the 18-month follow-up period, 1.81% of the SARS-CoV-2-positive children were diagnosed with asthma compared with 2.13% of SARS-CoV-2-negative children. Having a positive SARS-CoV-2 test result was not associated with the hazard of a new asthma diagnosis, although Black race, comorbid food allergy, and allergic rhinitis were. Among children aged 1 to 4 years, being born prematurely and having a higher BMI were also associated with greater risk of new asthma diagnosis. Among school-aged children and teenagers, being female increased risk.

In these electronic health record data from one institution, SARS-CoV-2 positivity did not predict risk of later asthma diagnosis.

COMMENT: This retrospective study did not demonstrate a correlation between COVID-19 diagnosis and new asthma diagnosis within 18 months of infection. Black race, food allergies, preterm birth, and BMI significantly increased the risk of asthma diagnosis, all of which are known factors. A large-scale prospective birth cohort study including COVID-19 among other viruses may further investigate the effect of COVID-19 on future respiratory conditions, including asthma.

S.M.K.

Senter JP, Aisenber LK, Dudley JW, et al. COVID-19 and asthma onset in children. Pediatrics. 2024;153:e2023064615.

Keywords: asthma (child), COVID-19

Early-Life Origins of Adult Cough

The prospective Tasmanian Longitudinal Health Study (TAHS) has been following participants in Tasmania, Australia, since 1968. In this latent class analysis of TAHS data, the study authors explored clinical characteristics from childhood to adulthood in participants with cough.

Of 3609 participants who returned the cough questionnaire when they were 53 years old, 2213 were defined as *current coughers*, meaning they answered "yes" to at least 1 cough-related question; 1396 did not report cough. The authors identified 6 subclasses of cough in current coughers: minimal cough, cough with colds only, cough with allergies, intermittent productive cough, chronic dry cough, and chronic productive cough. Asthma, gastroesophageal reflux disease, and chronic rhinosinusitis were most common in people with chronic dry cough or chronic productive cough. People with chronic productive cough also had the highest prevalences of smoking, chronic obstructive pulmonary disease, and depression.

The study describes the longitudinal trajectories of symptoms (eg, current productive cough, asthma, smoking) and lung function for people in the different cough subclasses from 7 to 53 years of age. About 49% of participants had current productive cough at 7 years of age, which decreased to about 11% at 13 years. Current productive cough after 13 years of age was highest in the subclasses of respondents with chronic productive cough, intermittent productive cough, and cough with allergies. The trajectories of FEV_1 and the ratio of FEV_1 to forced vital capacity were worse in people in the chronic productive cough and intermittent productive cough subclasses than in people with minimal cough. Compared with that in people with minimal cough, asthma prevalence from 7 to 53 years of age was higher in all other cough subclasses.

In summary, lung function trajectories were worse in people with chronic productive cough and intermit- • • •

tent productive cough, in whom the lifetime prevalences of productive cough, asthma, and allergies were increased.

COMMENT: In this unique prospective study, researchers examined longitudinal clinical characteristics and lung function trajectories of cough sufferers in a community-based cohort. The authors' analysis and identification of 6 cough subclasses advances our understanding of this heterogeneous condition and will help guide management and future research.

S.W.S.

Zhang J, Lodge CJ, Walters EH, et al. Association of novel adult cough subclasses with clinical characteristics and lung function across six decades of life in a prospective, community-based cohort in Australia: an analysis of the Tasmanian Longitudinal Health Study (TAHS). Lancet Respir Med. 2024;12:129-140.

Keywords: cough, lung function

Is Sublingual Tablet Administration in the Vestibular Space Better?

Up to 7% of patients stop taking their sublingual immunotherapy (SLIT) tablets because of reactions like throat irritation, swelling in the mouth, and itching in the mouth, ear, or tongue. This pilot study compared the tolerability of allergen immunotherapy (AIT) tablets administered in the vestibular region (the groove between the lower lip and the gingiva of the inferior teeth) or under the tongue.

Adults with allergic rhinitis/conjunctivitis were treated with vestibular or sublingual AIT tablets for birch pollen, grass pollen, ragweed pollen, or house dust mite allergy for 28 days, and local treatment-related adverse events (TRAEs) were assessed.

A total of 164 patients were randomly assigned: 83 in the sublingual group and 81 in the vestibular group. More patients in the vestibular group than in the sublingual group discontinued treatment because of adverse events (12% compared with 4%). Although more patients in the vestibular group experienced severe TRAEs, the difference between groups was not significant. Vestibular administration was more likely to result in lip swelling. Two participants in the vestibular group experienced anaphylaxis. Anecdotally, the authors reported that in some patients in the vestibular group, the tablets took more than 5 minutes to dissolve. More participants in the sublingual group reported that they would be "definitely willing" or "probably willing" to apply an AIT tablet in the same way as in the study.

The study authors concluded that the sublingual route should remain the standard.

COMMENT: The optimal location for immunotherapy in the oral cavity has been debated for decades. The vestibular mucosa has been considered a viable option because it contains fewer mast cells, which may lead to fewer adverse effects. This well-conducted study showed better tolerability with immunotherapy tablets administered in the sublingual space than with vestibular administration. The findings should remind clinicians to continue to evaluate their patients' SLIT technique to promote long-term use of a proven therapy. Of note, this study was funded by ALK, which does produce several SLIT products.

S.R.J.

Simard ML, Novak N, Drolet JP, et al. Tolerability of sublingual versus vestibular allergy immunotherapy tablet administration: a randomized pilot study. Clin Exp Allergy. 2024;54:120-129.

Keywords: allergen immunotherapy, sublingual immunotherapy tablet

The Link Between Inducible Laryngeal Obstruction and Mental Health

Patients with inducible laryngeal obstruction (ILO) experience anxiety and other behavioral health conditions that can affect their treatment outcomes. To further explore these associations, the authors assessed the prevalence of anxiety, depression, posttraumatic stress disorder (PTSD), and somatic physical symptoms in a cross-sectional sample of 83 adult and 81 pediatric patients with ILO.

As shown by data extracted from their medical records, children and adults with ILO had elevated rates of previously diagnosed anxiety, depression, and PTSD. At the time of their ILO diagnosis, 63% of adults and 60% of pediatric patients had anxiety according to their Screen for Adult Anxiety Related Disorders (SCAARED) or Screen for Child Anxiety Related Disorders (SCARED) scores, respectively. PHQ-9 (Patient Health Questionnaire-9) scores indicated that 32% of adults and 30% of pediatric patients had major depressive disorder. PTSD was suggested in 34% of adults and 16% of pediatric patients. Adults were twice as likely to present with PTSD. Forty-five percent of adults and 39% of children scored in the moderate to severe range for physical somatic symptoms.

The dyspnea that results from ILO is distressing to patients, and rates of anxiety, depression, and PTSD are elevated in this population. Future research could examine ways to coordinate the treatment of ILO and behavioral health conditions.

COMMENT: Previous retrospective studies have shown a link between ILO (also historically referred to as vocal cord dysfunction or paradoxical vocal fold motion) and mental health conditions such as anxiety and depression. This notably larger study prospectively screened patients who presented for ILO therapy for mental health disorders and found much higher rates of anxiety and PTSD than in earlier studies for both adults and children. Allergists, who are often the first to recognize ILO, should keep in mind that treating both the physical laryngeal symptoms and the mental health component is essential for optimal outcomes.

S.R.J.

Fujiki RB, Fujiki AE, Thibeault SL. Anxiety, depression, and posttraumatic stress disorder in patients with induced laryngeal obstruction. JAMA Otolaryngol Head Neck Surg. 2024;150:368-377.

Keywords: inducible laryngeal obstruction, mental health

Mental Health Concerns of Patients With Food Allergy

This study analyzed real-world survey data from the Food Allergy Research & Education (FARE) Patient Registry to better understand the impact of food allergies on patient and caregiver mental health.

Data were for 1680 US residents who reported at least one food allergy and completed a survey on mental health concerns. The survey sample was mostly White (79%), 61% female, and 55% pediatric patients. A total of 62% of respondents reported mental health concerns. Patients experienced anxiety about living with food allergies (55%) and after an allergic reaction (46%). Caregivers reported being afraid to trust others with their child (56%) and fearing for their child's safety (56%).

Patients who experienced a greater number of reactions per year, had a single food allergy, were not admitted to the hospital, or were racial or ethnic minorities had a greater likelihood of experiencing mental health concerns related to their food allergy. Patients who had received a formal mental health diagnosis were less likely to report mental health concerns.

One-third of patients reported that they would like to be screened for mental health concerns. Among those who were screened, nearly three-quarters were asked informal questions during their allergy appointment; less than one-quarter completed a formal test or questionnaire. Patients whose parent completed the survey were more likely to have a formal mental health diagnosis.

The survey findings support mental health screening for patients with food allergies. Suggested assessment tools include the Food Allergy Independent Measure, the Pediatric Food Allergy Quality of Life Questionnaire, the Scale of Food Allergy Anxiety, and the Scale of Psychosocial Factors in Food Allergy.

COMMENT: Are we doing enough to address the psychosocial burden of food allergy? The findings of this analysis suggest that patients and caregivers are at risk for mental health concerns related to food allergies. Notably, one-third of patients indicated they would like to be screened. The authors offer several assessment tools that clinicians can use to address this unmet need.

S.W.S.

Casale TB, Warren C, Gupta S, et al. The mental health burden of food allergies: insights from patients and their caregivers from the Food Allergy Research & Education (FARE) Patient Registry. World Allergy Organ J. 2024;17:100891.

Keywords: food allergy, mental health

Do Ultraprocessed Foods Increase Risk for Food Allergy?

The incidence of food allergy in children is increasing, and diet could play a role. Children today consume more ultraprocessed foods, which contain advanced glycation end products (AGEs). Through in vitro and clinical investigations, the authors explored the effects of AGEs on gut barrier integrity, inflammation, immune responses, and mitochondrial function and the accumulation of AGEs in the skin.

In human enterocytes, exposure to AGEs altered the integrity of the gut barrier, increased the production of IL-25 and IL-33, and increased the production of RAGE (receptor for advanced glycation end products) and reactive oxygen species. In biopsy samples of the small intestine, AGE treatment activated inflammation and the release of the proinflammatory cytokines IL-6 and tumor necrosis factor-α. In peripheral blood mononuclear cells from children at risk for atopy, AGE exposure increased the number of late apoptotic cells, reduced the cell proliferation rate, increased the production of Th2 and proinflammatory cytokines, and altered mitochondrial metabolism.

As estimated from food intakes reported in 7-day food diaries, intakes of the 3 most common glycation products found in a Western diet were higher in children with food allergy than in healthy control children. Children with food allergy also had greater accumulation of AGEs in their skin.

The study findings provide support for a role of dietary AGEs in food allergy. The authors conclude that as a preventive measure against food allergy, children's exposure to dietary AGEs should be limited.

COMMENT: Ultraprocessed foods often undergo cooking at high temperatures, which leads to protein and lipid glycation and the creation of AGEs. This in vitro study finds that AGE exposure reduces gut barrier integrity, induces innate immune system activation, and increases Th2 cytokine production. Children with food allergy appear to consume more AGEs and have higher levels of AGEs in their skin, suggesting a potential link between AGE consumption and food allergy.

G.B.L.

Paparo L, Coppola S, Nocerino R, et al. How dietary advanced glycation end products could facilitate the occurrence of food allergy. J Allergy Clin Immunol. 2024;153:742-758.

Keywords: advanced glycation end products, diet, food allergy

Can Blood Transfusions Trigger Allergic Reactions in Children With Food Allergy?

In many cases of allergic transfusion reactions, the allergen responsible is unknown. Blood products may contain food allergens, and allergic transfusion reactions are more common in children than in adults. Given this background, these authors were interested in studying whether food allergens in blood products can trigger allergic transfusion reactions in children.

The authors conducted basophil activation tests (BATs) using basophils collected from children with allergies to egg, milk, or wheat and sera from healthy donors collected 2 and 4 hours after the donors consumed 3 raw eggs, 500 mL milk, or 3 slices of bread.

Children with egg allergy had increased BAT scores when donor serum collected after egg ingestion was used. Increased BAT levels were associated with increased levels of IgE to egg white and a history of anaphylaxis. Children with milk and wheat allergies showed responses to only one of the donor sera.

BAT responses varied according to the time that elapsed between consumption of the food by the blood donor and blood collection, by donor, and by type of food ingested. The study did not verify concentrations of allergens in donor blood. Future studies are needed to examine the link between allergen contents in blood products and risk for allergic transfusion reactions.

COMMENT: Allergic transfusion reactions are IgE-mediated reactions against components in the donor's blood. This study finds that healthy donors who consume allergenic foods 4 hours prior can induce basophil activation in children with food allergy. Therefore, there may be a theoretical risk of a transfusion reaction due to food allergens in donor blood, although further studies are needed to quantify this risk.

G.B.L.

Yanagisawa R, Koike Y, Usami Y, et al. Activation of basophils in children with food allergies by blood from donors ingesting the corresponding food. Allergy. 2024;79:1602-1605.

Keywords: food allergy, transfusion reaction

IgE to CCDs May Be Associated With Grass Pollen Sensitization

Many patients with IgE-mediated allergic disease develop antibodies to what are known as cross-reactive carbohydrate determinants (CCDs), but the relevance of IgE to CCDs in childhood is not well studied. These authors examined IgE response to CCDs in a cross-sectional study of Italian children with seasonal allergic rhinitis and in a longitudinal birth cohort of German children.

Of the 1263 Italian children, 22% had IgE to CCDs. Children with IgE to CCDs experienced more oral allergy syndrome and gastrointestinal symptoms but less anaphylaxis than children without IgE to CCDs. IgE levels to CCDs were more closely related to extracts of Timothy and Bermuda grasses than other pollens.

Of 612 participants in the birth cohort followed up at 20 years, 3.9% had IgE to CCDs. Age at first detection of IgE to CCDs ranged from 2 to 20 years, and once started, the IgE response persisted in 95% of the participants.

The study concluded that IgE to CCDs is common in patients with pollen allergy, is associated with a strong IgE response to grass pollen, emerges with sensitization to grass group 1 and 4 allergens, can start at an early age, and once started persists.

COMMENT: Anti-CCD IgE antibodies remain a prominent cause of false positives in assays evaluating aeroallergen sensitization in both pediatric and adult patients. This study out of Italy and Germany is a key reminder of this false-positive risk but also shows that these antibodies often develop in childhood, especially in close association with grass pollen sensitization. Skin testing remains a reasonable approach in those suspected of false positives due to the presence of anti-CCD IgE. It has been proposed that mast cell degranulation during skin testing is less likely to occur in response to CCDs (and therefore less likely to lead to false-positive results) owing to the lower affinity of IgE to CCDs and/or the presence of CCD-specific IgG-blocking antibodies.

S.R.J.

Potapova E, Tripodi S, Panetta V, et al. IgE to cross-reactive carbohydrate determinants (CCD) in childhood: Prevalence, risk factors, putative origins. Clin Exp Allergy. 2024;54:195-206.

Keywords: allergic rhinitis, CCD, grass pollen

Consider Autoantibodies to IL-23 in Adults With Recurrent Opportunistic Infections

Autoantibodies to cytokines are recognized to increase susceptibility to severe infections. Many patients with thymoma have autoantibodies against IL-12 (anti-IL-12), but not all these patients develop opportunistic infections. This study examined the role of autoantibodies against IL-23 (anti-IL-23), a cytokine that controls inflammation in the skin, lungs, gastrointestinal tract, joints, and brain, in opportunistic infection in these patients.

In a discovery cohort, the authors screened for anti-IL-23 in 30 patients with anti-IL-12 antibodies (vs 30 healthy control participants). In the 30 patients with anti-IL-12 (83% of whom had thymoma), anti-IL-23 was found in 77%, • • •

but not all autoantibodies had neutralizing activity. Neutralization of IL-23–induced STAT3 phosphorylation occurred in 50% of patients and correlated with the severity of infection.

In a larger validation cohort of 91 patients with thymoma, who were likely to have autoantibodies against both IL-12 and IL-23, 26% had IL-23 binding activity and 19% showed inhibition of IL-23–induced STAT3 phosphorylation.

The authors then screened 128 other patients with other severe infections for anti-IL-23. Anti-IL-23 binding was found in 19% of patients with severe intracellular infections, 12% of patients with unusual intracranial infections, and 10% of patients with invasive mold infections. Two of the 16 patients with intracranial infections had anti-IL-23 neutralizing activity in the absence of autoantibodies to IL-12.

In patients with thymoma, the presence of neutralizing anti-IL-23 was a discriminating factor determining which patients experienced invasive infections, which suggests that IL-23 protects against cellular and extracellular pathogens.

COMMENT: A phenocopy of a primary immunodeficiency is caused by somatic mutations or anti-cytokine antibodies that are often missed by genetic testing. This study identifies anti-IL-23 autoantibodies as the cause of invasive and opportunistic infections due to candida, pneumocystis, pseudomonas, klebsiella, and mycobacteria species. B cell depletion via rituximab induced clinical remission in infections, underlying the importance of thinking beyond genetic panels when evaluating patients with immunodeficiencies to target the underlying cause.

G.B.L.

Cheng A, Kashyap A, Salvator H, et al. Anti-interleukin-23 autoantibodies in adult-onset immunodeficiency.
N Engl J Med. 2024;390:1105-1117.

Keywords: autoantibodies, opportunistic infections, thymoma

Early Recognition of IgE-Mediated Perioperative Anaphylaxis

Although rare, perioperative anaphylaxis, which is the most severe form of perioperative immediate hypersensitivity, can result in death. This retrospective observational cohort study examined risk factors for this life-threatening IgE-mediated allergy.

For 145 patients with suspected perioperative immediate hypersensitivity, data were collected from medical records, through review of anesthetic charts, and through anesthesiologist interviews. For the analysis, patients with positive skin test results to a suspected trigger, increased histamine levels, or increased tryptase levels were put in the IgE-mediated allergy group. Patients with negative results were put in the non-allergy group.

Most patients in the IgE-mediated allergy group had positive skin test results to neuromuscular blocking agents or β-lactam antibiotics. Most events occurred immediately before or immediately after the induction of anesthesia.

The study identified 4 distinct cutaneous phenotypes in patients with suspected perioperative immediate hypersensitivity:

- lack of cutaneous signs—the reference;
- early cutaneous vasodilation—visible as localized or generalized erythema, extensive urticaria, and palpebral or labial angioedema;
- early cutaneous vasoconstriction—visible as pallor, localized or generalized piloerection, thelerethism, and sweating with or without cyanosis; and
- late cutaneous vasodilation—visible as localized or generalized erythema and extensive urticaria.

Early cutaneous vasoconstriction was the most important risk factor for IgE-mediated allergy, and late cutaneous vasodilation was the most useful factor supporting a diagnosis of allergy. The best-fit model containing the cutaneous phenotypes, low mean arterial pressure of 60 mm Hg or less, and low end-tidal CO_2 of 25 mm or less had an area under the curve of 0.91.

Early recognition of the clinical presentation of perioperative anaphylaxis can allow timely bedside diagnosis and treatment.

COMMENT: This study identified early cutaneous vasoconstriction, which occurred in only life-threatening reactions, as the strongest predictor of a life-threatening IgE-mediated reaction. Such symptoms include piloerection, thelerethism, pallor, sweating, and cyanosis, which are not the typical findings most clinicians associate with anaphylaxis. Educating anesthesia, surgical, and operating room staff to assess skin and recognize the various cutaneous signs of an IgE-mediated reaction may guide prompt treatment.

S.M.K.

Dewachter P, Mouton-Faivre C, Dimby SF, Vicaut E, Beloucif S. Association between early patient characteristics and IgE-mediated allergy in the perioperative setting.
J Allergy Clin Immunol Pract. 2024;12:1202-1214.

Keywords: allergic reaction, anesthesia

Real-World Adherence to Anaphylaxis Guidelines in Older Adults Low

In parallel with an increase in Western countries, the incidence of anaphylaxis has increased in Asian populations. Data are lacking, however, on real-world physician adherence to anaphylaxis guidelines for children, adults, and older adults. This retrospective study from Taiwan assessed emergency department (ED) physician adherence to anaphylaxis guidelines between 2001 and 2020.

Information on the ED management of 771 • • •

patients with anaphylaxis (159 children, 498 adults, and 114 older adults) was extracted from electronic medical records. Outcomes of interest were physician adherence to (1) epinephrine administration, (2) allergist referral, (3) education on avoiding triggers, and (4) education on symptoms.

Epinephrine was administered to 51% of patients with anaphylaxis. The highest rate of administration was in children (47%); the lowest rate was in older adults (30%). Among patients with moderate anaphylactic reactions, only 14% of older adults received intramuscular epinephrine compared with 35% of adults and 55% of children. Concerning the other study outcomes, only 15% of patients received an allergist referral, 13% of patients received education on avoiding triggers, and 16% of patients received education on symptoms.

The authors conclude that real-world adherence to anaphylaxis guidelines in the ED remains suboptimal, especially in the treatment of older adults.

COMMENT: The ED is often where patients present for anaphylaxis care, and adherence to anaphylaxis guidelines in this setting is essential to ensure lifesaving care. To this end, allergists have engaged in anaphylaxis education efforts, and adherence to anaphylaxis guidelines, particularly administration of first-line epinephrine, has increased from 2001 to 2020. Despite improvements in care, gaps still exist in epinephrine administration, allergist referral, and patient education. This study found that gaps in care were pronounced in patients 65 years of age and older, highlighting a need to ensure that future educational efforts around anaphylaxis recognition and management are inclusive of this age group.

I.M.O.

Ho CH, Lee HJ, Yeh YH, et al. Physician adherence to anaphylaxis guidelines among different age groups in emergency departments: 20-year observational study.

Ann Allergy Asthma Immunol. 2024;132:519-524.

Keywords: anaphylaxis, guidelines

Atopy, Asthma, and COVID Susceptibility

Is type 2 inflammation in allergic disease a risk factor for severe COVID-19 outcomes? Using a large claims database, these authors addressed this question in 2 patient cohorts: (1) a COVID-19 susceptibility cohort consisting of patients with and without allergic conditions and (2) a cohort with confirmed COVID-19. The allergic conditions studied included asthma, atopic dermatitis, allergic rhinitis, eosinophilic esophagitis, food allergy, and anaphylaxis.

In the susceptibility cohort, the incidence rate of COVID-19 was higher in patients with allergic conditions than in those without, and this association remained after adjustment for prognostic variables like age, sex, race/ethnicity, body mass index, and health care resource utilization. The adjusted incidence rate ratio for COVID-19 was higher in patients with severe asthma than in those with nonsevere asthma.

Among patients with COVID-19, the 30-day risk for hospitalization or all-cause mortality was higher in patients with asthma than in those with other allergic conditions, even after adjustment for prognostic variables like race/ethnicity, prior COVID-19 vaccination, and recent use of immunosuppressants. The risk for all-cause mortality was lower in the adjusted model for patients with allergic conditions than in those without.

Having an allergic condition may elevate risk for diagnosis of COVID-19 but reduce mortality after infection.

COMMENT: This is another study that provides important information to share with our atopic patients regarding their risks associated with COVID-19. Although patients with atopic conditions were more likely to receive a diagnosis of COVID-19, the risk for mortality after infection was lower. Patients with asthma, on the other hand, had higher risk for COVID-19–related hospitalization and all-cause mortality.

V.H.T.

Chen C, Song X, Murdock DJ, et al. Association between allergic conditions and COVID-19 susceptibility and outcomes.

Ann Allergy Asthma Immunol. 2024;132:637-645.

Keywords: allergy, COVID-19, type 2 disease

Melatonin: the Newest Anti-Inflammatory Agent?

Mast cells are an integral part of the immune system but when over-activated contribute to allergic disease, chronic urticaria, and irritable bowel syndrome. In this letter, the authors report on their study of the effects of melatonin in an RBL-2H3 cell line overexpressing MRGPRX2, a mast cell receptor. They found that pretreatment of cells with melatonin inhibited the release of β-hexosaminidase, a marker of mast cell activation, in a concentration-dependent manner from cells stimulated with compound 48/80. Pretreatment of cells with melatonin also reduced the secretion of tumor necrosis factor-α and IL-6 in MRGPRX2-expressing cells stimulated with compound 48/80.

The authors suggest that melatonin may not only target the rapid degranulation that occurs during the first phase of mast cell activation but also attenuate cytokine release during the second phase.

COMMENT: The authors describe that melatonin can effectively suppress rapid mast cell degranulation. At higher concentrations, more anti-inflammatory effects were noted. Further studies are needed to investigate clinical efficacy in mast cell disorders.

V.H.T.

Ye H, Cheng P, Jin B, Xu H, Wang B. Melatonin inhibits mast

cell activation, indicating its potential as a therapeutic agent in inflammatory diseases.

Ann Allergy Asthma Immunol. 2024;132:659-661.

Keywords: mast cells, melatonin

Bullying Not Uncommon in Those With Atopic Dermatitis

How does stigma related to chronic skin disorders like atopic dermatitis (AD) affect the quality of life (QoL) of children and adolescents? The authors sought to answer this question by using validated tools for measuring stigma in children with chronic disease.

Tools included the PPS-Skin (Patient-Reported Outcomes Measurement Instrumentation System Pediatric Stigma supplement for children with skin conditions) and Proxy PPS-Skin (a measure for caregivers). Child-assessed stigma scores were compared with disease severity, QoL, anxiety, depression, poor peer relationships, and caregiver responses.

The study enrolled 1671 patient/caregiver dyads. About 58% of the children were female and 56% were White; their mean age was 13.7 years. Diagnoses included acne, AD, alopecia, and psoriasis. More than half of children reported that their condition was highly visible at all times.

Nearly three-quarters (73%) of the children reported stigma. For AD and ichthyosis, more than 10% of children reported high stigma. Girls reported more stigma than boys. Caregiver reports of bullying were associated with worse scores for stigma. Stigma scores were positively correlated with reduced QoL, depression, and anxiety and negatively correlated with peer relationships.

Children with chronic skin disease experience effects beyond measures of disease severity and visibility, and caregivers should be aware of stigma and its effects on QoL.

COMMENT: As clinicians, we often concentrate on disease severity metrics such as EASI (Eczema Area and Severity Index) or SCORAD (Scoring Atopic Dermatitis) when evaluating AD. Although QoL has been identified as a key patient outcome that should be considered in long-term management, stigmatization and bullying are often not fully captured in the currently used questionnaires, such as the Dermatology Life Quality Index. This unique cross-sectional study showed that clinicians should be evaluating these additional metrics in children, especially girls, when the lesional skin is visible and not covered by clothing or when the patient has a more severe phenotype. Additional medical and psychological interventions may be warranted in these children to improve their QoL.

S.R.J.

Paller AS, Rangel SM, Chamlin SL, et al. Stigmatization and mental health impact of chronic pediatric skin disorders.

JAMA Dermatol. Published online April 24, 2024.

Keywords: atopic dermatitis, quality of life

Neonatal Airway Colonization and Later Risk for Asthma and Allergy

The authors previously reported that children whose airways are colonized with certain bacterial species when they are infants have an increased risk for persistent wheeze and asthma until 5 years of age. Here they examine associations between airway colonization with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* and asthma and allergy in children up to 18 years of age.

About 21% of the infants' airways were colonized with at least 1 of the bacteria studied. Children with neonatal airway colonization had a higher risk for wheeze/asthma until age 7. The difference in risk was greatest at age 4 and disappeared by age 12 to 18. Colonization increased the risk for a persistent wheeze/asthma phenotype before 3 years of age and was associated with an increased number of exacerbations until age 7 and increased blood eosinophils and tumor necrosis factor-α until age 12.

Bacterial colonization of the neonatal airway was associated with an early onset of persistent wheeze/asthma, but these associations were attenuated by the time the children reached school age.

COMMENT: How does the microbiome of the neonatal upper airway impact wheezing/asthma phenotypes later in life? These authors evaluated 3 bacterial species and found significant associations with asthma development and exacerbations early in life that did not persist beyond early grade school. This timing corresponds with a common clinical phenotype, "upper respiratory infection–associated wheeze," seen in toddlers and early school-aged children that resolves as children age. Notably, a tiny fraction of the airway microbiome was assessed, and the authors do not report concomitant rates of other infections such as RSV or rhinovirus, which may confound or interact with the airway microbiome to contribute to clinical phenotypes.

T.G.C.

Sunde RB, Thorsen J, Kim M, et al. Bacterial colonisation of the airway in neonates and risk of asthma and allergy until age 18 years.

Eur Respir J. 2024;63(1):2300471.

Keywords: asthma, microbiome, wheeze