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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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Pharmacokinetics of Dry Powder Intranasal Epinephrine Spray

Epinephrine is universally recommended to treat anaphylaxis, but the currently available injectable forms are underused. The dry powder intranasal epinephrine spray FMXIN002 was developed as a needle-free alternative to intramuscular epinephrine autoinjectors.

This open-label trial compared the pharmacokinetics, pharmacodynamics, and safety of FMXIN002 spray with those of an intramuscular autoinjector (EpiPen) in 12 adults (3 women and 9 men) with seasonal allergic rhinitis without asthma.

Pharmacokinetic responses varied among individuals. After a nasal allergen challenge, T_{max} was shorter after administration of the nasal spray (3.2 mg epinephrine) than after the intramuscular autoinjector (0.3 mg epinephrine), but not significantly so. T₁₀₀ (the time when the measured

analyte concentration was 100 pg/mL during the absorption phase) was shorter for the nasal spray. C_{max} and the area under the curve from 0 to 8 hours were higher after treatment with the nasal spray compared with the intramuscular autoinjector, but these differences were not significant. The most common adverse events after administration of the nasal spray were application-site erythema, headache, and nasal congestion. No adverse events were reported after administration of the autoinjector. The spray was stable at room temperature for up to 2 years.

A needleless epinephrine delivery system may overcome some of the barriers to uptake of injectors, such as high cost and low adherence. Powder-based and liquid-based intranasal administration products are under development. The authors suggest that powder-based formulations like FMXIN002 may be better distributed in the nasal cavity. Future studies with larger populations and higher doses are planned to address interpatient variability in response. ● ● ●

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COMMENT: The results of this open-label trial of a dry powder intranasal epinephrine spray are intriguing. While this trial provides important pharmacokinetics, pharmacodynamics, and safety data, the sample was small and homogeneous, and the study did not directly evaluate the use of this therapy in anaphylaxis. Phase II and III trials are needed to determine whether this represents an acceptable alternative to intramuscular epinephrine for our patients.

S.W.S.

Tal Y, Ribak Y, Rubin L, et al. Fast acting, dry powder, needle-free, intranasal epinephrine spray: a promising future treatment for anaphylaxis.

J Allergy Clin Immunol Pract. 2023;11(10):3047-3054. ●

Keywords: allergic rhinitis, epinephrine, immediate hypersensitivity, nasal sprays

Oral Food Challenge: What Happens in the Real World?

Oral food challenge (OFC) is the reference method for diagnosing food allergy. Although the testing can improve a patient's quality of life and establish threshold reactivity doses for future oral immunotherapy, OFC is underused in clinical practice. To document real-world experience with OFC, this observational study explored the outcomes of all OFCs conducted in a single integrated health services organization over 3 years.

The 3 allergy and immunology outpatient offices studied performed 1132 OFCs: 528 to confirm or refute a food allergy diagnosis, 295 to test whether a food allergy had resolved, 184 to study tolerance to baked milk or egg, and 125 by family request. The patients' mean age was 4 years and about 60% were male.

About 76% of patients tolerated the food in the challenge, 21% experienced a reaction, and 3% refused the food and did not complete the challenge. The most tolerated food was shellfish (tolerated in 35 of 38 OFCs, or 91%); foods with the lowest percentages of tolerance were baked egg (66%), sesame (68%), wheat (69%), and peanut (69%). In OFCs considered to be high risk, the test food was tolerated in 53% of tests.

Among patients who experienced a reaction, 30% did so after the first dose. Most (54%) patients who experienced a reaction were treated with an antihistamine alone; 29% were treated with epinephrine. No patients required a third epinephrine dose or additional treatment in the emergency department.

The patient characteristics predicting tolerance to OFC were older age, smaller skin-prick testing wheal, smaller skin-prick testing flare, and lower food-specific IgE (both at diagnosis and at the time of the challenge). Children with a history of peanut allergy were less likely to tolerate OFC.

The findings suggest that OFCs can be safely conducted in an outpatient allergy and immunology office not physically connected to an inpatient facility and that certain patient characteristics can predict tolerance.

COMMENT: While patients and families may understandably have concerns regarding OFCs, this article gives us important information about these tests in the real-world setting. Overall, the chal- ● ● ●

lenges were tolerated by most patients. In those with reactions, most had urticaria or angioedema and did not require epinephrine. Patients with less reactive skin testing, lower food-specific IgE, and older age at challenge were more likely to tolerate a food challenge.

V.H.T.

Mustafa SS, Bress J, Capucilli P, et al. Outcomes of oral food challenges in a real-world setting, with predictors of outcomes.

Ann Allergy Asthma Immunol. 2023;131(5):655-660. ●

Keywords: food allergy, oral food challenge

Skin Testing Refractory Period After Food-Induced Allergic Reaction

Skin prick testing (SPT) is often delayed for 4 to 6 weeks after an acute food-induced allergic reaction because of a presumed refractory period during which the risk for false-negative results is increased. Data supporting this practice are limited.

These authors report on a prospective study of SPT in patients with a history of food allergy to milk, egg, peanut, or hazelnut. Food allergy was confirmed by single-blind, placebo-controlled food challenge, and SPT was performed at baseline, 1 to 2 hours, 1 to 2 weeks, and 30 to 40 days after the induced allergic reaction.

Data from 34 patients aged 5 to 34 years were included. SPT was performed on all patients at the first 2 time points, in 19 patients at 1 to 2 weeks, and in 9 patients at 30 to 40 days.

SPT wheal size decreased from baseline to 1 to 2 hours and then increased from 1 to 2 hours to 1 to 2 weeks. The increase in wheal size corresponded to an increase in test sensitivity from 71% at 1 to 2 hours to 95% at 1 to 2 weeks. There were no differences between measures at 1 to 2 weeks and those at 30 to 40 days, between baseline and 1 to 2 weeks, or between baseline and 30 to 40 days.

The authors conclude that SPT performed at 1 to 2 weeks is highly sensitive. The main limitation of the study was the high attrition rate.

COMMENT: The practice of delaying SPT is largely based on data from venom and drug allergy skin testing. In this well-conducted study, SPT performed 1 to 2 hours after a reaction did show significantly lower measurements, possibly because of impaired skin mast cell degranulation and histamine release. Interestingly, test sensitivity reached 95% at 1 to 2 weeks post-reaction, which is a notably shorter refractory phase than is seen in drug or venom allergy. Delaying testing for 4 to 6 weeks is likely unnecessary after food-related allergic reactions. Retesting patients with negative SPT results at 1 to 2 weeks after their acute reaction may be indicated if clinical suspicion remains high.

S.R.J.

Mulé P, Prosty C, Mazer B, et al. Duration of skin prick test refractory

period following food-induced allergic reactions.

Clin Exp Allergy. 2023;53(10):1059-1061. ●

Keywords: food allergy, skin tests

Predicting Treatment Response to Viaskin Peanut Epicutaneous Immunotherapy

The Efficacy and Safety of Viaskin Peanut in Children With IgE-Mediated Peanut Allergy (PEPITES) study showed Viaskin Peanut epicutaneous immunotherapy (EPIT) to be well tolerated with durable peanut desensitization. This analysis examined whether biomarkers could predict response in participants of the phase 3 clinical trial.

Effects of EPIT on levels of serum-specific IgG4 and IgE (whole peanut and the peanut proteins Ara h 1, 2, 3, 8, and 9) were studied in 301 children (201 in the EPIT group and 100 in the placebo group).

Changes in IgE levels were larger in the EPIT group than in the placebo group, especially levels of Ara h 1 IgE at 3 months. Peanut IgG4, Ara h 1 IgG4, and Ara h 2 IgG4 and the peanut IgG4:IgE increased from baseline to 12 months in the EPIT group but not the placebo group.

In the univariate analysis, the parameter with the highest area under the curve for predicting treatment responders was the serum-specific IgG4:IgE at 12 months. Using a positive predictive value threshold of 80% to calculate cutoffs, the investigators determined that IgG4:IgE >20.1 at 12 months could predict a post-treatment reaction threshold of 300 mg. In the multivariate model, the best predictors of post-treatment reaction thresholds were peanut IgG4:IgE and Ara h 1 IgE.

The findings suggest that daily EPIT with 250g peanut protein elicits a similar immune response trajectory to that of oral and sublingual immunotherapy, and the treatment effect is seen by 3 months. IgG4:IgE at 12 months and Ara h 1 IgE have potential as biomarkers of treatment response that do not require daily peanut ingestion.

COMMENT: These authors analyzed serum-specific IgG4 and IgE levels for whole peanut and peanut components in peanut-allergic children drawn at baseline, 3, 6, and 12 months to assess relationships with responder outcomes. Peanut IgG4 and IgE levels in children receiving peanut EPIT followed a similar trajectory to that observed with other forms of immunotherapy and could distinguish those treated with EPIT versus placebo. Additionally, a specific IgG4:IgE and Ara h 1 sIgE level each had moderate predictive value for treatment response. This exploratory study adds to a growing body of work investigating immunotherapeutic options for patients with food allergies.

S.W.S.

Bastin M, Carr WW, Davis CM, et al. Immune response evolu- ● ● ●

tion in peanut epicutaneous immunotherapy for peanut-allergic children. *Allergy*. 2023;78(9):2467-2476. ●

Keywords: epicutaneous immunotherapy, IgE, IgG4, peanut allergy, Viaskin Peanut

α-Tryptase Genotype Associated With Severe Food Allergy

It remains difficult for clinicians to predict the severity of food allergy. In other allergic reactions, elevated copy numbers of the gene encoding α-tryptase are associated with reaction severity. These authors studied α-tryptase isoforms and allergy severity in patients with an IgE-mediated food allergy.

Tryptase genotyping was performed in 119 participants in 2 study cohorts. In the National Institute of Allergy and Infectious Diseases cohort (NIAID), all 3 patients with hereditary α-tryptasemia (HαT) had a history of anaphylaxis. Participants with α-tryptase had higher Severity Grading Score for Acute Reactions (SGSAR) scores (NS) and were more likely to have a history of food-related anaphylaxis.

In the peanut allergy cohort, 2 of 21 participants with severe reactions had HαT. About 17% of participants (1 of 6) with only the β-tryptase isoform had a severe reaction during a peanut oral food challenge, whereas 65% of participants (20 of 31) with the α-tryptase isoform had a severe reaction. α-Tryptase copy number was correlated with SGSAR and Bock/Practical Allergy symptom scores. The results of allergy testing (eg, skin-prick testing, peanut-specific IgE levels) did not differ according to copy number of α-tryptase isoforms.

Presence of the α-tryptase isoform is correlated with more severe food allergy reactions. The authors suggest that tryptase genotyping has advantages over serum tryptase levels as a biomarker because gene sequencing can be done noninvasively and eliminates the need for multiple serum measurements before, during, and after an acute allergic reaction.

COMMENT: The tryptase gene *TPSAB1* encodes for α- and β-tryptase isoforms, and increased copy number of α-tryptase is the cause of HαT. This study of food-allergic children found an association between the α-tryptase genotype and severe food-allergic reactions, which also occurred in all 5 patients with HαT. If these findings are replicated in larger trials, the α-tryptase genotype could be used as a biomarker to predict risk of severe food allergy.

G.B.L.

Lang A, Kubala S, Grieco MC, et al. Severe food allergy reactions are associated with α-tryptase.

J Allergy Clin Immunol. 2023;152(4):933-939. ●

Keywords: food allergy, hereditary α-tryptasemia, α-tryptase

Do Food Allergens Play a Role in Eosinophilic Gastroenteritis?

Eosinophilic gastrointestinal disorders are rare immune-mediated conditions in which eosinophils infiltrate the gastrointestinal causing abdominal pain, nausea, vomiting, weight loss, and diarrhea. The pathogenesis of eosinophilic gastritis/gastroenteritis (EoG/EoGE) is poorly understood, and treatment options other than corticosteroids are needed. This study evaluated treatment with a diet free of food allergens (an elemental formula) in 15 adults with confirmed EoG/EoGE.

Adults (47% male) were treated with an amino acid-based formula for 6 weeks (study products included Neocate Junior and Neocate Splash [Nutricia] and EleCare Jr [Abbott]). Histologic remission was defined as less than 30 eosinophils per high-power field in the stomach and duodenum.

All participants experienced complete histologic remission. Other significant effects included a decrease in overall Physician Global Assessment score, improved Eosinophilic Gastritis Reference Score, and improved scores on an Eosinophilic Gastritis Diagnostic Panel (derived from the expression of 18 dysregulated genes). Treatment also improved patient-related and quality of life outcomes, specifically the Severity of Dyspepsia Assessment (SODA) pain intensity, non-pain, and satisfaction scores and the Patient-Reported Outcomes Measurement Information System Adult Profile 29 (PROMIS) depression score. The article also reports analyses of serum cytokines and chemokines (NS) and changes in the stool microbiome with treatment.

Foods were reintroduced in 13 participants, 11 of whom underwent follow-up endoscopy showing histologic recurrence. One participant with renal insufficiency developed hyponatremia.

The study findings suggest a role of food allergens in the pathogenesis of EoG/EoGE and support the use of dietary therapy. The study authors note that such therapy “should be pursued by a trained team with proper dietary support” and that the cost of therapy be considered.

COMMENT: This prospective trial of elemental formula in patients with EoG/EoGE demonstrates remission of disease with a food-allergen-free diet with relapse of disease after food reintroduction. Unfortunately, multiple food triggers (including those beyond a 6-food elimination diet) were identified, making empiric elimination diets unlikely to be successful.

G.B.L.

Gonsalves N, Doerfler B, Zalewski A, et al. Prospective study of an amino acid-based elemental diet in an eosinophilic gastritis and gastroenteritis nutrition trial.

J Allergy Clin Immunol. 2023;152(3):676-688. ●

Keywords: eosinophilic gastritis, eosinophilic gastroenteritis, elemental diet, food allergy

Clues to Differentiating FPIES and Immediate-Type Food Allergy

Some of the gastrointestinal symptoms of immediate-onset food allergy (FA) in adults overlap those of food protein-induced enterocolitis syndrome (FPIES), a non-IgE-mediated food allergy. Because treatment of the 2 disorders in the emergency department differs, the authors sought to delineate their clinical presentations in a Japanese population.

The authors reviewed patients' electronic health records and then followed up with them by phone using a standardized questionnaire to diagnose FPIES and FA. In 73 adults who avoided crustaceans and were successfully contacted, 8 were determined to have FPIES and 53 to have FA. About 21% of the patients with FA had gastrointestinal symptoms.

Patients with FPIES experienced a longer latency period after ingestion of the causative food, had symptoms longer, and were more likely to have digestive symptoms. They were also more likely to have a history of gastrointestinal disorders. When the authors compared patients with FPIES with patients with FA and gastrointestinal symptoms, they found that patients with FPIES were older at the time of their first episode, experienced more intense pain, and were more likely to have abdominal distension.

Alaskan pink shrimp, white leg shrimp, and red king crab were the most common species that elicited food allergy. Patients with FPIES were more likely than those with FA to have an allergy caused by lobster.

The authors suggest that the differences they identified in the clinical presentation of adult FPIES and FA are a first step toward developing a diagnostic algorithm for use in the emergency department.

COMMENT: When patients initially present with food reactions, it can be challenging to parse out immediate-onset FA from FPIES, particularly when gastrointestinal symptoms predominate. Clues that point toward FPIES include a longer latency after ingestion (median 2.3 vs 0.3 hours) and longer duration of symptoms (mean 20.8 vs 13.2 hours). Between FPIES patients and FA patients with gastrointestinal symptoms, FPIES patients reported significantly more severe colic pain and abdominal distention as well as more syncope and fear of death. However, incidence of nausea, vomiting, and diarrhea did not differ. This study provides insight into key questions for differentiating between immediate-onset FA and FPIES.

I.M.O.

Watanabe S, Sato A, Uchida H, et al. Comparison of adult food protein-induced enterocolitis syndrome to crustaceans and immediate-type food allergy.

Ann Allergy Asthma Immunol. 2023;131(4):487-493.e2. ●

Keywords: food allergy, FPIES

Home-Based Spirometry May Not Be Equal to Clinic Spirometry

In the post-COVID-19 era, more patient visits for asthma management are being conducted remotely with use of portable spirometers. However, consistent data are lacking on how well home and clinic spirometry measures agree. This post hoc analysis assessed agreement between home and clinic measures of trough FEV₁ in patients with uncontrolled asthma.

Data were from 2436 patients in the phase 3A CAPTAIN trial (NCT02924688) and 421 patients in the phase 2B 205832 trial (NCT03012061), both of which assessed the addition of umeclidinium to a medication regimen. Patients were trained by study staff to perform spirometry at home with an AM3 device (eResearch Technology) that integrated an electronic diary with a peak flowmeter.

In both trials, treatment improved FEV₁ whether measured at home or in the clinic. However, the at-home measures of trough FEV₁ were lower than the clinic measures and were less consistent. As shown by Bland-Altman plots, agreement between home and clinic measures was poor at baseline and 24 weeks in both trials.

When the data were analyzed using agreement thresholds, nearly one-third of patients had trough FEV₁ measures that differed by 0.25 to 0.5 L between the clinic and home (28% of patients in the CAPTAIN trial and 31% of those in 205832 trial). Measures differed by 0.5 to 1 L in 14% and 20% of patients in the 2 trials, respectively.

This is the largest post hoc comparison to date of home and clinic spirometry. The authors suggest that agreement between measures could be improved with more systematic training of patients in how to perform home spirometry, including retraining, monitoring, and real-time instruction.

COMMENT: Mobile spirometry and remote patient monitoring are important tools in asthma management and will become more widely utilized in the coming years. However, several studies and a meta-analysis published in the past few years have consistently shown a significant discrepancy between home spirometry and supervised clinic spirometry measurements. This post hoc analysis suggests that unsupervised home readings are not interchangeable with supervised clinic measurements, specifically for asthma patients. Before home spirometry can be widely accepted in asthma, additional studies are needed to optimize patient training and to better understand this discrepancy between home and clinic measurements.

S.R.J.

Oppenheimer J, Hanania NA, Chaudhuri R, et al. Clinic vs home spirometry for monitoring lung function in patients with asthma.

Chest. 2023;164(5):1087-1096. ●

Keywords: asthma, pulmonary function test, spirometry

Does Preexisting Chronic Rhinosinusitis Predict New-Onset Asthma?

Because of the low annual incidence of asthma, answering such as this requires a large sample size. These authors studied whether prevalent chronic rhinosinusitis (CRS) is associated with new-onset asthma in the following year by using electronic health record (EHR) data from the Geisinger integrated health system.

To be eligible, adults had to have contact with the health system in 2 or more years no more than 4 years apart. The study sample had a mean age of 45.2 years, and 67% were female. CRS was identified in 2 ways: by sinus computed tomography (CT) scan text in radiology reports and by 2 CRS diagnosis entries in the EHR on different days. Asthma was identified by 2 diagnoses for asthma or one diagnosis plus one order for an asthma medication.

A total of 35,441 persons diagnosed with new-onset asthma were compared with 890,956 persons without an asthma diagnosis. Of 2897 persons with a positive sinus CT scan, 49.2% were female; 97.1% were White, and mean age was 49.7 years. A total of 15,717 persons were identified by diagnoses. Their mean age was 48.8 years; 57% were female, and 97.5% were White.

Variables associated with a diagnosis of new-onset asthma included female sex, Black race, Hispanic ethnicity, being a current user of tobacco, and having ever received medical assistance (ie, Medicaid). Persons with allergic rhinitis, gastroesophageal reflux disease, obstructive sleep apnea, or a history of eosinophilia were also more likely to be diagnosed with new-onset asthma.

Both definitions of CRS were associated with new-onset asthma, although the associations were attenuated when sinus surgery was added to the model. The findings may have implications for asthma prevention.

COMMENT: This longitudinal cohort study analyzed EHR data and radiologic findings for over 900,000 individuals over an 11-year span and found that sinonasal inflammation is an independent risk factor for the development of asthma. In the CRS group, the association for new onset asthma was strongest in those with a positive sinus CT scan report. These findings add to our understanding of the natural history of CRS; however, the question of whether we can prevent future development of comorbidities in CRS patients remains unanswered for now.

S.W.S.

Schwartz BS, Pollak JS, Bandeen-Roche K, et al. Sinus inflammation and chronic rhinosinusitis are associated with a diagnosis of new onset asthma in the following year. *Allergy*. 2023;78(10):2659-2668. ●

Keywords: asthma etiology, epidemiology, rhinosinusitis

Asthma Impairment and Risk Questionnaire to Assess Asthma Control

Risk factors for asthma exacerbations are less likely to be addressed if a patient's asthma control is overestimated. The authors compared the performance of the Asthma Impairment and Risk Questionnaire (AIRQ), the Asthma Control Test (ACT), and physician and patient assessment for evaluating asthma control.

Ratings of asthma control were similar between patients and physicians for ratings of completely and well-controlled asthma but not for ratings of poorly or not controlled asthma. Only 26% of patients who were assessed by physicians to have poorly or not controlled asthma assessed themselves similarly. ACT scores indicated that 49% of patients had well-controlled asthma and 25% had very poorly controlled asthma. With use of the AIRQ, only 35% of patients were assessed as having well-controlled asthma; 27% were rated as having very poorly controlled asthma. One or more exacerbations were experienced by 5% of patients rated with well-controlled asthma by the AIRQ compared with 14% of patients rated similarly by the ACT.

The authors conclude that the AIRQ was as good as or better than patients and physicians and better than the ACT for correctly classifying patients who had experienced an exacerbation in the previous year. Use of the tool may improve patient assessment.

COMMENT: Accurate assessments of asthma control can be challenging and overly optimistic, contributing to the ongoing asthma health care burden in the United States. This study suggests that using the AIRQ may improve assessments of asthma control. It may be time to start using the AIRQ more in clinical practice.

I.M.O.

Chippis B, Zeiger RS, Beuther DA, et al. The Asthma Impairment and Risk Questionnaire enhances the assessment of asthma control. *Ann Allergy Asthma Immunol*. 2023;131(4):436-443.e1. ●

Keywords: asthma, asthma control, disease exacerbation

Further Analysis of Tezepelumab for Severe Uncontrolled Asthma

A further analysis of pooled data from the PATHWAY (NCT 02054130) and NAVIGATOR (NCT 03347279) trials of tezepelumab in patients with severe, uncontrolled asthma examined the efficacy and safety of tezepelumab in clinically relevant subgroups.

In the overall patient population (n = 1334), the annualized asthma exacerbation rate was reduced by 60% with tezepelumab. Reductions ranged from 40% in ●●●

patients with fractional exhaled nitric oxide (FeNO) levels less than 25 ppb to 78% in patients with blood eosinophil counts greater than or equal to 450 cells/ μ L. In patients with and without perennial aeroallergen sensitivity, tezepelumab reduced the exacerbation rate by 62% and 54%, respectively. Tezepelumab also reduced exacerbations compared with placebo in patients grouped by combinations of blood eosinophil counts, perennial allergy status, and FeNO levels. In patients with “triple” type 2 (T2)-low disease (blood eosinophil count <150 cells/ μ L, FeNO levels <25 ppb, and without perennial allergies), the reduction was 34%.

Exacerbations associated with hospitalization or emergency department visits were reduced by 79% in the overall group and by 60% to 94% in all subgroups studied. Tezepelumab improved prebronchodilator FEV₁ in the overall population, in combined biomarker subgroups, and in patients with and without perennial allergies. Incidence of adverse effects did not differ significantly between tezepelumab and placebo.

By combining data from the PATHWAY and NAVIGATOR trials, the authors were able to study the effects of tezepelumab in clinically relevant subgroups with greater statistical precision. Tezepelumab reduced exacerbations across subgroups, including in patients with T2-high or T2-low inflammation.

COMMENT: Tezepelumab’s claim to fame has been as the first biologic approved for severe asthma regardless of T2 inflammation, a welcome addition to the allergist’s armamentarium given limited options for severe T2-low asthma. However, don’t sleep on tezepelumab for T2-high patients, as the greatest decrease in annualized asthma exacerbation rates were seen in patients with the highest peripheral eosinophil counts and FeNO. Notably, in this pooled analysis, the authors provide the performance of tezepelumab in subgroups with combinations of 2 or 3 biomarkers, which may help in counseling patients more precisely on expected benefits.

T.G.C.

Corren J, Menzies-Gow A, Chupp G, et al. Efficacy of tezepelumab in severe, uncontrolled asthma: pooled analysis of the PATHWAY and NAVIGATOR clinical trials.

Am J Respir Crit Care Med. 2023;208(1):13-24. ●

Keywords: asthma (adult), asthma (severe), exacerbations

Differentially expressed miRNAs were identified and characterized according to clinical features and tissue and immune cell expression.

High-quality nasal miRNA data were from 575 infants, 27% of whom developed asthma by 6 years of age. A total of 23 differentially expressed miRNAs were associated with asthma risk, and the risk was higher in infants with respiratory syncytial virus (RSV) infection. A heat map is presented showing the association of 18 differentially expressed miRNAs with asthma-related clinical features like infant history of eczema, corticosteroid use, and RSV or rhinovirus infection. Differentially expressed miRNAs were highly expressed in lung, spleen, bone marrow, and all immune cells. In the gene pathway analysis, asthma-related signaling pathways were enriched in infants who developed childhood asthma.

A study limitation is that only the nasal airway was sampled, although bronchiolitis also involves inflammation of the lower airways. Also, the nasal specimens could have been contaminated with blood immune cells, which would affect the miRNA profiles.

Nasal miRNAs were associated with asthma risk and asthma-related clinical features in infants with severe bronchiolitis. The study findings may further research into asthma preventive strategies that focus on miRNA.

COMMENT: The complex intersection of early environmental exposures, such as infections, with underlying individual genetic predisposition in the development of asthma warrants the extensive attention it has received. This study demonstrated associations of differentially expressed nasal miRNAs in infants hospitalized for bronchiolitis with later asthma development, suggesting another mechanistic link driven by environmental exposure through post-transcriptional gene regulation. Further study is needed to tease out the specific impacts of these identified miRNAs. Characterization of the underlying mechanisms may lead to preventive targets.

T.G.C.

Zhu Z, Freishtat RJ, Harmon B, et al. Nasal airway microRNA profiling of infants with severe bronchiolitis and risk of childhood asthma: a multicentre prospective study. Eur Respir J. 2023;62(2):2300502. ●

Keywords: asthma (child), bronchiolitis

MicroRNA Profile in Infants With Bronchiolitis at Risk for Asthma

About 30% of infants with bronchiolitis requiring hospitalization develop asthma later in childhood, but the mechanism of this association is unknown. To study this relation, the authors performed microRNA (miRNA) sequencing of nasal swab samples collected from infants hospitalized for bronchiolitis at 17 medical centers in the United States.

Housing Assistance to Improve Childhood Asthma Outcomes

Black children are disproportionately affected by asthma, and living in a resource-poor neighborhood contributes to this disparity. Individual- or household-level interventions are often not successful in improving asthma morbidity because they do not address neighborhood-level causes.

The Mobility Asthma Project (MAP) was a prospective cohort study to determine whether moving from a ● ● ●

resource-poor to a low-poverty neighborhood could reduce asthma morbidity in Baltimore City children. The program enrolled 123 children with persistent asthma or an asthma exacerbation in the past 12 months, of whom 106 moved to new homes. Study children were matched with 115 children in the Urban Environment and Childhood Asthma birth cohort.

The mean age of the MAP cohort was 8.4 years; 47% of the children were female and 98% were Black. After moving, the odds of asthma exacerbation was reduced by 54%. Expressed as a rate, there were 0.88 exacerbations (defined as the number of times a child used an oral or intramuscular corticosteroid burst in the past 3 months) per person-year before moving and 0.40 per person-year after (a 70% decrease). The number of days that children experienced symptoms in a 2-week period decreased from 5.1 before moving to 2.7 after. Moving reduced the odds of having a symptom day by 59%. The reductions in exacerbations and symptoms were not mediated by reductions in home environmental exposures to mouse allergen or indoor particulate matter but were mediated by neighborhood factors like social cohesion, perceptions of safety, and caregiver stress (29%–35%).

A program that assisted families in moving to low-poverty neighborhoods resulted in reductions in asthma symptoms days and exacerbations in participant children. The findings support policies addressing neighborhood-level factors to improve children's health.

COMMENT: Previous studies have shown structural racism, which includes residential redlining, to be a significant cause of asthma disparities. However, few studies have examined the utility of programs meant to target structural racism as a mechanism to improve childhood asthma outcomes. The improvements in asthma symptoms and exacerbation frequency reported here were driven by reduced psychological stressors and not by indoor particulate matter (allergens or irritants). Outdoor allergens were not considered, which is a major limitation as high-poverty neighborhoods are often closer to highways with higher particulate matter concentrations. Allergists should understand the various factors that contribute to asthma control. While pharmacotherapies remain a vital part of our treatment toolkit, psychological stressors, particularly associated with housing, should also be considered.

S.R.J.

Pollack CE, Roberts LC, Peng RD, et al. Association of a housing mobility program with childhood asthma symptoms and exacerbations.

JAMA. 2023;329(19):1671-1681. ●

Keywords: asthma (children), health disparities, social determinants of health

Disparities in Asthma Care and Prevalence

Black and Latinx adults are disproportionately affected by asthma but lack access to specialty care. Whether telehealth

and in-person visits have similar outcomes in Black and Latinx adults is unknown. For this ancillary study of the PREPARE (Person Empowered Asthma Relief) trial, surveyed participants by email and phone about their visit type preferences.

A total of 847 trial participants completed the survey, and about 56% reported both in-person and telehealth visits for asthma care. For regular asthma care checkups, 42% of participants preferred telehealth, 49% preferred in-person visits, and 9% had no preference. For new or worsening asthma symptoms, 19% preferred telehealth, 75% preferred in-person visits, and 6% had no preference. For asthma emergencies, the corresponding percentages were 8%, 89%, and 3%. When asked to consider circumstances like cost, time away from work, arranging family care, and transportation, participants preferred telehealth over in-person visits when considering transportation factors.

A subset of 98 patients completed 2 or more monthly surveys about asthma control variables and had electronic health record data available. The characteristics associated with their telehealth use included sex, ethnicity, employment status, controller therapy regimen, and number of emergency department visits or asthma-related hospitalizations in the year before enrollment. Asthma control and asthma-related quality of life did not differ according to whether asthma care was exclusively in-person or included telehealth.

Slightly over half of Black and Latinx adults surveyed preferred telehealth for regular asthma care checkups, and asthma outcomes were similar regardless of the type of visit. This is the first study to examine patient preferences for telehealth according to race and ethnicity. The findings lend support to continuing the availability of telehealth for regular asthma checkups.

Although data from the National Health Interview Survey (NHIS) indicate that the overall prevalence of asthma did not change significantly from 2006 to 2018, disparities in prevalence persist. To better understand asthma prevalence among US children and adults, analyzed NHIS data from 2019 to 2021.

Outcome variables were current asthma, asthma attacks, and emergency department or urgent care visits. Associations between asthma outcomes and demographic and socioeconomic factors were analyzed in multivariable logistic regression models.

About 6.4% of children had current asthma. Prevalence was higher in males and non-Hispanic Black children. Children with public health insurance coverage, with family difficulty paying for a child's medical bills or prescription medication, whose family received rent assistance, or with family income less than 100% of the federal poverty threshold (FPT) were more likely to have asthma. Children with family difficulty paying medical bills or with family income less than 100% FPT were more likely to have asthma attacks.

About 8% of adults had current asthma. Prevalence was higher in women and in non-Hispanic Black adults. Adults having difficulty paying for medical bills or prescription ● ● ●

medication, difficulty obtaining medical care, or having family income less than 100% FPT or 100% to 199% FPT were more likely to have current asthma and asthma attacks.

The study findings confirm that asthma measures intersect with demographic and socioeconomic factors. Recognizing and addressing the factors that influence health is vital for improving asthma outcomes.

COMMENT: We may be trying for our patients with asthma, but differences persist! These articles highlight the disparities that exist among patients of different races or ethnicities with asthma in the United States. The authors remind us that increased public health efforts are needed to address these disparities. Telehealth was useful for visits among Black and Latinx patients and was preferred by these patients for regular checkups. These are important studies that identify and recommend solutions that may aid in addressing disparities to improve medical care among all our patients with asthma.

V.H.T.

Ugalde IC, Ratigan A, Merriman C, et al. Preference for and impact of telehealth vs in-person asthma visits among Black and Latinx adults.

Ann Allergy Asthma Immunol. 2023;131(5):614-627. ●

Pate CA, Qin X, Johnson C, Zahran HS. Asthma disparities among U.S. children and adults.

J Asthma. 2023;60(12):2214-2223. ●

Keywords: asthma, health disparities, telehealth

Neighborhood-Level Factors in Early Life Affect Asthma Incidence

Neighborhood-level factors are known to contribute to childhood asthma, but few studies have examined how exposure at different life stages affects asthma incidence. Using measures in the Child Opportunity Index (COI) and Social Vulnerability Index (SVI), this study examined asthma at different life stages in children participating in the Environmental Influences on Child Health Outcomes (ECHO) Program.

Geospatial software was used to geocode the children's home addresses, and parents or caregivers reported a child's diagnosis of asthma at infancy, in childhood, and in adolescence. A total of 10,516 children from 46 ECHO cohorts were included. The overall asthma incidence rate was 23.3 cases per 1000 child-years.

Asthma incidence was associated with COI at birth, during infancy, and during early childhood, with lower incidence rate ratios in areas with higher opportunity scores. In children with high or moderate COI at birth, incidence rate ratios for asthma were 0.87 (when compared with very low COI at birth). Associations with SVI were not significant after adjust-

ment but were in the hypothesized directions. Incidence rate ratios for the association of COI with asthma were attenuated after adjustment for early childhood body mass index.

Neighborhood opportunity measures were associated with asthma incidence. The lack of significance of the associations with the SVI may be because that index was developed for use in emergency preparedness, whereas the COI incorporates neighborhood characteristics more relevant to child health. Because the cohorts included in the analysis were distributed throughout the United States, the findings may be more generalizable to the US population than previous studies. The study results add more evidence for a link between neighborhood conditions in early life and childhood asthma.

COMMENT: This cohort study found that neighborhood opportunity and vulnerability factors contribute to the incidence of pediatric asthma. Asthma rates were lower in areas with higher opportunity and vulnerability indexes, though hypothesized to be related to health, environmental, social, and economic domains and not education. These studies are crucial to primary prevention of asthma and offer areas for further improvement in healthy food access, exercise programs, pollution, and neighborhood safety.

S.M.K.

Aris IM, Perng W, Dabelea D, et al. Neighborhood opportunity and vulnerability and incident asthma among children.

JAMA Pediatr. 2023;177(10):1055-1064. ●

Keywords: asthma (childhood), health equity

Socioeconomic Status-Food Quality Relation in Children With Food Allergy

Socioeconomic status (SES) is known to be associated with the quality of children's diets, but whether this is also the case in children with food allergy was previously unstudied. The authors explored the association of SES with diet quality in a cross-sectional study of children with IgE-mediated food allergy (n = 92) and a control group of children without food allergy (n = 81).

Parents completed a food-frequency questionnaire, and these data were used to calculate the children's nutrient intakes. The authors then used the Diet Quality Index-International (DQI) to convert intakes into diet quality scores. Parental education and income were used to assign SES categories (high or low).

Overall scores on the DQI-I and subscores describing diet variety and diet adequacy differed according to SES, with higher scores in children with high vs low SES. Among the 8 subcomponents of the adequacy score, children with high SES had higher intakes of vegetables, fruit, fiber, and vitamin C (beta-coefficients ranging from 0.6 to 1.6 and false- ● ● ●

discovery rate <0.5). No SES–food allergy interaction effect was found.

The study results confirm that SES is associated with diet quality, with children from high-SES households having diets that were more varied and more adequate. Because of the low number of children with food allergy and low SES, additional studies with larger samples are needed.

COMMENT: This study examined a group of children with a high proportion of food allergy and demonstrated a positive association between SES and diet quality. These results highlight 2 important points: (1) Children with food allergy must seek safe alternatives, and often the alternatives are more expensive. Increasing access to a variety of healthy foods is essential to proper growth, safety, and prevention of disease. (2) Access to a dietitian for those with food allergies may assist with a unique patient-centered plan for a safe balanced diet and resources to locate those foods in a cost-effective manner.

S.M.K.

Vo TVA, Irizar H, Gibson K, et al. Socioeconomic status and diet quality in children with and without food allergy.

J Pediatr. 2023;260:113337. ●

Keywords: dietary patterns, food allergy, social class

CTCL-Like Reaction Associated With Dupilumab for Atopic Dermatitis

Dupilumab, which blocks the interleukin-4 receptor α (IL-4R α), is increasingly used in the treatment of atopic dermatitis. As its use has increased in real-world settings, several case reports have described the development of cutaneous T-cell lymphomas (CTCLs), a malignant condition. Because benign lymphoid reactions (LRs) can mimic CTCLs, the authors sought to characterize the histopathologic features of LR associated with dupilumab treatment.

This was a retrospective observational case series of 14 adults in the Netherlands suspected of having CTCL while being treated with dupilumab. Skin biopsy samples collected before, during, and at least 3 months after dupilumab treatment were evaluated by an experienced dermatopathologist. After biopsy review, 3 of the 14 patients were diagnosed with mycosis fungoides (MF), a relatively rare CTCL. The remaining 11 patients were determined to have LR. All 14 patients initially responded to dupilumab before their symptoms worsened. Some patients with LR reported burning or painful skin as a new symptom.

Histopathologically, LR cases showed no loss of CD2, CD3, or CD5, whereas MF cases showed loss of CD2 and CD5. LR cases showed CD30 overexpression. Dupilumab was discontinued in all patients, and those with LR showed clinical improvement. Follow-up data were not available for all the patients with MF.

It is important for clinicians to recognize and assess LR in patients treated with dupilumab. The authors conclude, “the study highlights the need for caution in continuing dupilumab treatment in patients with AD [atopic dermatitis] with clinical worsening and newly reported symptoms.”

COMMENT: Biologics have become a vital therapeutic option, and dupilumab is frequently prescribed because of its efficacy and multiple medical indications. Unmasking and accelerating MF has been a concern with dupilumab treatment because of the theoretical risk of increased free IL-13 availability when IL-13 signaling is blocked by dupilumab. This allows IL-13 to bind to a lesser-known IL-13R α 2 that is associated with the progression of MF. Whereas MF is generally considered irreversible and often progressive, LR frequently resolve after discontinuation of dupilumab. Practicing allergists should be aware that dupilumab can both unmask MF and cause clinically similar LR. Patients should be monitored closely because LR remain poorly understood and may be an initial step in the development of CTCL.

S.R.J.

Boesjes CM, van der Gang LF, Bakker DS, et al. Dupilumab-associated lymphoid reactions in patients with atopic dermatitis.

JAMA Dermatol. 2023;159(11):1240-1247. ●

Keywords: atopic dermatitis, cutaneous T-cell lymphoma, histopathology

Reassuring Patients With Chronic Urticaria About Booster Vaccination

Many patients with chronic urticaria (CU) have concerns about COVID-19 vaccination. Using real-world data from Urticaria Centers of Reference and Excellence (UCAREs), this retrospective study assessed disease exacerbations and allergic reactions after COVID-19 vaccination in adults with CU.

Among 2769 patients, 9% experienced vaccination-induced exacerbation of their disease. In 223 patients with exacerbation after the first vaccine dose, about 53% also experienced exacerbations after the second dose. CU was treated mainly with antihistamines. Exacerbation was more common in patients with fever, fatigue, muscle and joint pain, or headache after vaccination.

Risk factors for exacerbation were being female, having disease duration less than 24 months, having chronic spontaneous (vs inducible) urticaria, receiving an adenovirus viral vector vaccine, having nonsteroidal anti-inflammatory drug (NSAID)/aspirin intolerance, and having concerns about getting vaccinated. Risk was lower in those treated with omalizumab and in Hispanic patients.

Exacerbations occurred in only a small number of patients with CU. The authors offer suggestions for managing COVID-19 vaccinations in these patients, such as ensuring that the patient’s disease is under control, refraining from use of NSAIDs, and offering omalizumab. ● ● ●

COMMENT: Allergists are often queried about urticaria risk after vaccination. Although optimal preventive strategies remain unclear, increased caution may be prudent in patients with prior COVID-19 vaccine-induced CU and constitutional symptoms (fever, muscle pain, joint pain, headache) and in patients with aspirin/NSAID intolerance. Reassurance may not only be needed but be therapeutic, as patient concern about being vaccinated was associated with CU exacerbations. Patients can be reassured that local reactions are not associated with more frequent exacerbations. Exacerbations lasted for a few days in 46% of patients, but some exacerbations did last a few weeks (24%) or even a few months (23%). This study provides interesting insights into which of our CU patients may be at greater risk of developing CU exacerbation after vaccination.

I.M.O.

Kocatürk E, Salameh P, Sarac E, et al. Urticaria exacerbations and adverse reactions in patients with chronic urticaria receiving COVID-19 vaccination: results of the UCARE COVAC-CU study.

J Allergy Clin Immunol. 2023;152(5):1095-1106. ●

Keywords: chronic urticaria, COVID-19 vaccine booster

Clinical Characterization of Children With Selective IgM Deficiency

Selective IgM deficiency (SIgMD) is an inborn error of immunity characterized by IgM levels less than 2 SDs of values in healthy persons of the same age or an absolute value less than 20 mg/dL in children. This observational study evaluated clinical symptoms and immunologic data in 48 children with SIgMD in Italy.

The children were diagnosed at a mean age of 8.9 years, and 83% were male. Children were about 5 years old when they first experienced symptoms, and the average delay in diagnosis was 3.8 years. The predominant clinical manifestation of disease was infection, specifically bronchitis (31% of the study children), pharyngitis (27%), and otitis (27%). Next most predominant were allergic conditions, primarily atopic dermatitis (27%) and allergic rhinitis (25%). Twelve patients (25%) were being treated with antihistamines or corticosteroid inhalers. Most patients had no immunologic abnormalities other than reduced serum IgM. In 16 patients followed for a mean of 4 years, SIgMD persisted, and in 2 patients IgA levels decreased.

The study authors suggest that a complete immunological workup is warranted in children diagnosed with SIgMD and that these patients be followed up so that their clinical condition can be monitored.

COMMENT: SIgMD, a more recently classified inborn error of immunity, appears to affect males more than females and commonly manifests with recurrent infections, allergies, and/or autoimmune disease. This multicenter study of a cohort of Italian pediatric patients recommended that

workup be comprehensive in patients with isolated low IgM levels and suggestive clinical history to gain further knowledge of additional immunologic abnormalities.

S.M.K.

Castagnoli R, Taietti I, Votto M, et al. Clinical and immunological phenotypes of selective IgM deficiency in children: results from a multicenter study. *Pediatr Allergy Immunol.* 2023;34(9):e14015. ●

Keywords: inborn errors of immunity, selective IgM deficiency

Patient-Reported Outcomes for Gefapixant

Gefapixant has been studied in phase 3 trials for the treatment of refractory chronic cough and unexplained chronic cough. In a letter to the editor, the study investigators report a pooled analysis of patient-reported outcomes for treatment with 45 mg gefapixant up to 52 weeks.

Patient-reported outcomes improved in both the placebo and gefapixant groups, with higher odds of improvement in the gefapixant group. More patients in the gefapixant group reported taste-related adverse effects (65% in the gefapixant group vs 7% in the placebo group) and discontinued treatment for this reason (14% vs 0.3%). For almost all patients, adverse events had resolved by the time the clinical trial database was locked.

Clinically meaningful improvements in patient-reported outcomes occurred with gefapixant treatment over 52 weeks. As in other trials, the placebo response through 52 weeks was robust.

COMMENT: Gefapixant for refractory or unexplained chronic cough has not performed as a management silver bullet, with the US Food and Drug Administration declining approval in 2022. Modest improvements were observed in the assessment of patient-reported outcomes from the phase 3 trials. However, these continue to be hampered by significant tolerability concerns, most notably taste disturbance, which is a significant factor in patient quality of life in other populations cared for by allergists and immunologists (eg, patients with chronic rhinosinusitis with nasal polyps). Don't hold your breath—the path to enter the US market will be challenging for gefapixant.

T.G.C.

Birring SS, Dicipinigaitis PV, Smith JA, et al. Efficacy and safety of gefapixant for refractory or unexplained chronic cough over 52 weeks. *Am J Respir Crit Care Med.* 2023;207(11):1539-1542. ●

Keywords: chronic cough, gefapixant, patient-reported outcome measures

Microbiome Data

Support Hygiene Hypothesis

The hygiene hypothesis suggests that household size, such as having more siblings, can protect against allergic disease. The mechanism of this association is unclear. Studies suggest that the rate at which the gut microbiome matures may affect allergy risk. The authors studied whether a protective effect on food allergy of having older siblings is mediated by maturation of the infant gut microbiota.

In a study cohort from southeastern Australia, fecal samples were collected from infants at 1 month, 6 months, and 1 year of age and food allergy testing was done at 1 year (skin-prick testing and food challenge). Fecal 16S rRNA sequence data were collected for at least 1 time point. The authors calculated microbiota-by-age z scores based on 16S rRNA sequence variants, with higher scores indicating a more mature gut microbiota. Data were also collected on the presence of pets or livestock in the household, birth delivery method, breast-feeding duration, and age at which solid food was introduced.

A higher microbiota-by-age z score at 1 year of age was associated with a reduced risk of food allergy. The effect was not driven by specific taxa of microorganisms. Having a higher number of siblings was associated with a higher z score at 1 year of age, as was having a dog in the home. The microbiota-by-age z score at 1 year of age mediated 63% of the protective effect of having more siblings and 27% of the protective effect of having a dog.

The study findings suggest that the mechanism by which having older siblings protects against food allergy may be advanced maturation of the infant gut microbiota.

COMMENT: Strachan's hygiene hypothesis was based on an epidemiologic observation that an increased number of siblings was protective against allergic disease in younger siblings. This birth cohort demonstrates that infants with more siblings have more mature gut microbiota and a decreased risk of food allergy. This study provides further evidence supporting the influential 1989 study.

G.B.L.

Gao Y, Stokholm J, O'Hely M, et al; BIS Investigator Group. Gut microbiota maturity mediates the protective effect of siblings on food allergy. *J Allergy Clin Immunol.* 2023;152(3):667-675. ●

Keywords: food allergy, gut microbiome

REVIEWS OF NOTE

COMMENT: The allergist/immunologist is often challenged with the diagnosis of vocal cord dysfunction (VCD), which is also called inducible laryngeal obstruction (ILO). This expert panel proposes consensus criteria for the recognition of VCD/ILO, which include throat tightness, symptoms only in the upper chest, rapid onset, inspiratory stridor, and lack of response to bronchodilators or inhaled steroids. Laryngoscopy with provocation is the gold standard test.

G.B.L.
Leong P, Vertigan AE, Hew M, et al; Vocal Cord Dysfunction/Inducible Laryngeal Obstruction Delphi Expert Panel. Diagnosis of vocal cord dysfunction/inducible laryngeal obstruction: an International Delphi Consensus Study. *J Allergy Clin Immunol.* 2023;152(4):899-906.

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