

The allergist and IgE: The realization that allergic diseases are not all IgE mediated

(Allergy Asthma Proc 42:183–186, 2021; doi: 10.2500/aap.2021.42.210037)

The discovery of immunoglobulin E (IgE) by the Ishizaka and Ishizaka¹ and Johansson² laid the groundwork for a fundamental paradigm shift in our understanding of allergic sensitization that has provided a harvest of improved diagnostic and therapeutic applications far beyond the dreams and expectations of their discoverers. Yet, in recent years, there has been a realization that not all allergic disease is IgE mediated. Several articles in this issue of the *Proceedings* address mechanisms of innate immune system injury, such as mast cell (MC) activation and neutrophil extracellular traps (NET), that contribute to non-IgE-mediated allergic diseases; these include non-IgE-mediated food allergy, non-atopic asthma, and drug allergy.

MCs have been implicated in a spectrum of allergic, immunologic, and infectious diseases that involve different organ systems. Whereas MC-related conditions such as clonal MC diseases and hereditary alpha tryptasemia have been well characterized, other MC-related disorders, such as MC activation syndrome (MCAS) and idiopathic anaphylaxis, remain poorly understood. Two articles in this issue address MCAS. Zhang and Bernstein³ provide a roadmap for clinicians to differentiate the myths and realities of MCAS, and to render an accurate diagnosis. One area that requires clarity is the alleged association between postural tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, and MCAS. In this issue, Wang *et al.*⁴ attempted to better define the co-occurrence of these diagnoses by analyzing 195 medical records of a single neurology department for the *International Classification of Diseases, Tenth Revision* (ICD-10) codes associated with disorders of autonomic dysfunction. The authors reported a high prevalence of MCAS ICD-10 codes (31%) among patients assigned ICD-10 codes for postural tachycardia syndrome and Ehlers-Danlos syndrome; however, it is unclear whether this observed association is true or can be attributed to diagnostic bias because vetting of the diagnostic criteria used by clinicians was not part of the analysis.⁴ Given these limitations, this intriguing association would benefit from more rigorous investigation.

In transitioning from MC disorders to food allergy, Bingol *et al.*⁵ classified 1248 children with food allergy from 26 different centers in Turkey based on underlying immune mechanisms of food hypersensitivity. The authors classified the mechanism to be IgE mediated in 71.8%, non-IgE mediated in 15.5%, and mixed IgE–non-IgE mediated in 12.7% of the patients. The most common food allergens identified were cow's milk, egg, tree nuts and/or peanut, wheat, and seafood (in order of decreasing frequency).⁵ The clinical findings of food allergy were highly variable, depending on age and underlying immune mechanism. Further exploring the underlying mechanisms of adverse food reactions is an article by König *et al.*,⁶ who performed a pilot study designed to convey the finding and relevance of mitochondrial DNA in the form of a NET as a new pathogenetic mechanism for innate immune-mediated non-IgE food allergy. Their novel analysis is intriguing and warrants future studies that evaluate the pathogenetic role of NETs in larger numbers of better characterized subjects with non-IgE food allergy.

Acute allergic reactions (AAR) to food occurs far too often in the real world. Two articles in this issue addressed the topic of AARs and their recurrence. In the first article, Robinson *et al.*⁷ reported on emergency department (ED) revisits and rehospitalizations for AARs among infants and toddlers. When using data from population-based multipayer, ED, and inpatient data bases (from New York and Nebraska) and when performing multivariable logistic regression, the authors conducted a retrospective cohort study of trends in ED visits and revisits, hospitalizations and rehospitalizations, and costs among infants and toddlers (age < 3 years) with an index ED visit or hospitalization for AAR (including anaphylaxis).⁷ They found that, between 2006 and 2015, infant and toddler ED visits for AAR increased by 27% per capita while hospitalizations for AAR remained stable.⁷ Factors most strongly associated with AAR ED revisits included the index visit hospitalization and receipt of epinephrine. The total costs for AAR ED visits and hospitalizations increased more than fourfold during the study period.⁷ In the second article, Yagmur *et al.*⁸ evaluated the recurrence of anaphylaxis and adrenaline autoinjector (AAI) use in childhood. At a single pediatric allergy/immunology clinic, a telephone survey

was conducted with the parents of pediatric patients who had been evaluated for anaphylaxis and prescribed AAI over a 4-year period.⁸ Their survey found that 22.5% of the 111 parents reported that their children experienced recurrent episodes of anaphylaxis.⁸ Among the parents with an AAI prescription, AAI use at the time of recurrent anaphylaxis was reported by only 42.3%.⁸ A variety of reasons were cited by the parents for not using AAI during an episode of anaphylaxis, the most common being a preference to have adrenaline administered at a health care facility because of its proximity and fear of using the device.⁸ The authors emphasized the importance of educating patients and families with regard to AAI use at each clinic visit to encourage the prompt and appropriate use of AAI immediately on anaphylaxis recognition.⁸

This issue features a preponderance of articles on the topic of asthma, including its burden of illness in the Gulf region, biomarkers, phenotypes, and targeted treatment with omalizumab. Alzaabi *et al.*⁹ investigated patients' perception with regard to asthma-related burden, their level of asthma control, and asthma management in three Gulf region countries (Saudi Arabia, United Arab Emirates, and Kuwait). Their article represented a subset analysis from the Asthma Insights and Management Survey in the Gulf and Russia. Consistent with findings from other studies of asthma control, the patients greatly overestimated their asthma control. Although 60.3% perceived their asthma as completely or well controlled, <1% of the patients actually met criteria for controlled asthma.⁹ In addition, substantial deficiencies in asthma management were identified, with only 30.5% of the patients given a lung function test and only 21.7% given a written asthma action plan.⁹

In transitioning from the burden of asthma to biomarkers and phenotypes, Zhao *et al.*¹⁰ aimed to explore the usefulness of the peripheral blood eosinophil count (PBEC) in assessing the level of fractional exhaled nitric oxide (FeNO) and predicting bronchodilation test results. The authors from a single medical center retrospectively analyzed the PBEC and bronchodilation test data of 384 outpatients who underwent FeNO measurement.¹⁰ They found that the PBEC had a predictive value for the FeNO level and bronchodilator reversibility test outcome and that it can be used as a simple and cost-effective predictor to assist in the diagnosis of type 2 asthma and assessment of airway inflammation.¹⁰

A less-studied asthma phenotype, the obesity phenotype, is addressed in this issue by van Zelst *et al.*,¹¹ who explored the association between elevated serum triglyceride levels and asthma in patients with obesity. Their hypothesis that higher lipid levels are more prevalent in patients with asthma and obesity was borne out in an explorative cohort study of 96 patients with asthma and 45 controls.¹¹ Their finding that elevated

serum levels of triglycerides were associated with the presence of asthma in patients with obesity indicated that elevated triglycerides might be a yet unrecognized trait that contributes to the development of asthma.¹¹ Because of the importance of this information, it was chosen as the basis for this issue's "For the Patient" section entitled "Association between elevated serum triglycerides and asthma in patients with obesity." This segment, found in the final pages of the print version of this issue and also available online, consists of a one-page article synopsis, written in a readily comprehensible fashion to help patients better understand the content of the full article.

In transitioning from asthma phenotypes to targeted biologic therapy, Papaioannou *et al.*,¹² provided a real-life study on the efficacy and safety of omalizumab in patients with allergic asthma. They presented a retrospective analysis of 45 patients treated with omalizumab for at least 8 years in four asthma clinics in Greece. Pulmonary function, asthma control, oral corticosteroid (OCS) dose, exacerbations, and adverse events were recorded before treatment (baseline), 6 months later, and annually thereafter.¹² Findings included a decrease in the annual exacerbation rate, from 4.1 at baseline to 1.1 after 1 year of treatment.¹² Of the 19 patients who were receiving OCS at baseline, 68.4% achieved 50% reduction after 2 years and more than two-thirds were able to completely discontinue OCS over 8 years.¹² The authors concluded that this real-life study of omalizumab treatment resulted in significant and sustained improvements in asthma exacerbations, asthma control, and lung function; had a steroid sparing effect; and a reasonable safety profile.¹²

Two articles addressed issues related to the upper airway, these being nasal polyps and aerobiology. Pan *et al.*¹³ evaluated nasal symptoms in an attempt to distinguish eosinophilic chronic rhinosinusitis with nasal polyps (eCRSwNP) from noneosinophilic nasal polyps based on PBECs. The authors prospectively enrolled 298 inpatients with CRSwNP and divided them into eCRSwNP and non-eCRSwNP groups based on a cut-off value of 3.05% blood eosinophils.¹³ The authors reported that nasal congestion and olfactory disorders were significantly different between the eCRSwNP and non-eCRSwNP groups. They concluded that the presence of an olfactory disorder might be the best nasal symptom to distinguish eCRSwNP from non-eCRSwNP.¹³

Although many allergists consider the ocean breeze as "free of allergens" and recommend visits to the coast for relief, it is important to verify this recommendation because of its potential implications on human health. Bielory *et al.*¹⁴ sought to provide this missing evidence by investigating the effect of sea breeze on spore dispersion between coastal and inland sites. They performed a comparison of mold spore counts

from Rotorod pollen samplers located at the Rutgers University Institute of Marine and Coastal Sciences (IMCS) Marine Field Station and 40 miles inland at the Rutgers University Pinelands Field Station (at a canopy height of 50 feet).¹⁴ Contrary to popular belief, the authors reported that there was no significant difference between the total spore concentration at the New Jersey coast and the New Jersey Pinelands canopy.¹⁴

In transitioning from the upper airway to hereditary angioedema (HAE), Ajewole *et al.*¹⁵ reviewed published data on short-term prophylaxis in pediatric patients with HAE. Their review examined first-line treatment options as well as the efficacy of off-label use of medications in this special patient population. Continuing with the theme of HAE, this issue also included a supplement that focuses on the HAE treatment burden in the context of the evolving treatment landscape. Banerji *et al.*¹⁶ reported on results from three independent corresponding surveys to understand the patient, caregiver, and physician experiences with managing HAE, and to identify factors that impact prophylaxis-associated treatment burden, overall well-being of patients and caregivers, and treatment preferences.^{17–19} These studies provide valuable insights into the patient, caregiver, and physician perspectives.

Coronavirus disease 2019 (COVID-19) continues to be a hot topic for the allergist/immunologist and has been a recurrent theme in past issues of the *Proceedings*.^{20–27} In this issue, Larenas-Linnemann *et al.*²⁸ explored the potential interplay among COVID-19, allergic diseases, and allergen immunotherapy (AIT). The authors reviewed the immune changes induced by AIT and shared their speculations with regard to the theoretical impact of these changes on the patient with allergy and infected with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). However, as they point out, the actual effect of AIT on the outcome of COVID-19 in patients with allergy remains to be determined.

In revisiting the topic of drug hypersensitivity, this issue's Patient-Oriented Problem Solving (POPS) case presentation explored the differential diagnosis of perioperative anaphylaxis in a 48-year-old woman with a cranial meningioma who was scheduled for surgery. The POPS case presentation is a recurring feature of the *Proceedings*, which, as per tradition, is written by an allergy/immunology fellow-in-training from one of the U.S. allergy/immunology training programs. The purpose of the POPS series is to provide an innovative and practical learning experience for the allergist/immunologist in-training by using a didactic format of clinical presentation and deductive reasoning. In this issue's POPS, Kolinsky and Lockey,²⁹ from the Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Morsani College of Medicine (Tampa, Florida), led the reader

through this learning process by illustrating the complexity of the differential diagnostic process for this clinical presentation and the importance of a detailed history, physical examination, and appropriate laboratory assessment in arriving at a correct diagnosis.

In summary, the collection of articles found within the pages of this issue further supports the realization that allergic, cutaneous, and respiratory disorders are not all IgE mediated, a finding that impacts the management of patients whom the allergist/immunologist serves. In particular, they exemplify how the complexities of MC disorders, food allergy, anaphylaxis, asthma, nasal polyps, aerobiology, HAE, COVID-19, and drug allergy continue to challenge the allergist/immunologist. In keeping with the overall mission of the *Proceedings*, which is to distribute timely information with regard to advancements in the knowledge and practice of allergy, asthma, and immunology to clinicians entrusted with the care of patients, it is our hope that the articles found within this issue will help foster enhanced patient management and outcomes. On behalf of the Editorial Board, we hope that you are able to make practical use of the diversity of literature offered in this issue of the *Proceedings*.

Joseph A. Bellanti, M.D. and
Russell A. Settipane, M.D.

REFERENCES

1. Ishizaka K, Ishizaka T. Identification of gamma-E-antibodies as a carrier of reaginic activity. *J Immunol* 1967; 99:1187–1198.
2. Bennich HH, Ishizaka K, Johansson SG, et al. Immunoglobulin E, a new class of human immunoglobulin. *Immunochemistry* 1968; 5:327–328.
3. Zhang S, Bernstein JA. Mast cell activation syndrome: myths and realities. *Allergy Asthma Proc*. 2021; 42:198–204.
4. Wang E, Ganti T, Vaou E, et al. The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers-Danlos syndrome. *Allergy Asthma Proc*. 2021; 42: 243–246.
5. Bingol A, Uygun DFK, Akdemir M, et al. Clinical phenotypes of childhood food allergies based on immune mechanisms: a multicenter study. *Allergy Asthma Proc*. 2021; 42:e86–e95.
6. König B, Koch AN, Bellanti JA. Studies of mitochondrial and nuclear DNA released from food allergen-activated neutrophils. Implications for non-IgE food allergy. *Allergy Asthma Proc*. 2021; 42:e59–e60.
7. Robinson LB, Arroyo AC, Cash RE, et al. Emergency department revisits and rehospitalizations among infants and toddlers for acute allergic reactions. *Allergy Asthma Proc*. 2021; 42:247–256.
8. Yagmur IT, Topal OY, Celik IK, et al. Evaluation of anaphylaxis recurrence and adrenaline autoinjector use in childhood. *Allergy Asthma Proc*. 2021; 42:e96–e100.
9. Alzaabi A, Idrees M, Behbehani N, et al. Patients' and physicians' attitudes and perception about asthma in the Gulf: a subset analysis from the Asthma Insights and Management Survey in the Gulf and Russia. *Allergy Asthma Proc*. 2021; 42:e77–e85.
10. Zhao B, Zheng H, Li X, et al. Evaluation of the peripheral blood eosinophil count as a predictor for fractional exhaled nitric

- oxide or bronchodilator reversibility test outcome. *Allergy Asthma Proc.* 2021; 42:228–234.
11. van Zelst CM, de Boer GM, Türk Y, et al. Association between elevated serum triglycerides and asthma in patients with obesity: an explorative study. *Allergy Asthma Proc.* 2021; 42:e71–e76.
12. Papaioannou AI, Mplizou M, Porpodis K, et al. Long-term efficacy and safety of omalizumab in patients with allergic asthma: a real-life study. *Allergy Asthma Proc.* 2021; 42:235–242.
13. Pan X, Zhang Y, Wang C, et al. Evaluation of nasal symptoms to distinguish eosinophilic from noneosinophilic nasal polyps based on peripheral blood. *Allergy Asthma Proc.* 2021; 42:214–221.
14. Bielory L, Bowers L, Marcus R, et al. The influence of sea breeze on mold spore dispersion. *Allergy Asthma Proc.* 2021; 42:222–227.
15. Ajewole O, Lanlokun M, Dimanchè S, et al. Short-term prophylaxis for children and adolescents with hereditary angioedema. *Allergy Asthma Proc.* 2021; 42:205–213.
16. Banerji A, Riedl MA, Craig TJ, et al. Insights into hereditary angioedema treatment burden in the evolving treatment landscape. *Allergy Asthma Proc.* 2021; 42(Suppl 1):S1–S3.
17. Radojicic C, Riedl MA, Craig TJ, et al. Patient perspectives on the treatment burden of injectable medication for hereditary angioedema. *Allergy Asthma Proc.* 2021; 42(Suppl 1):S4–S10.
18. Riedl MA, Craig TJ, Banerji A, et al. Physician and patient perspectives on the management of hereditary angioedema: a survey on treatment burden and needs. *Allergy Asthma Proc.* 2021; 42(Suppl 1):S17–S23.
19. Craig TJ, Banerji A, Riedl MA, et al. The caregiver role in managing HAE and their perceptions of treatment-related burdens. *Allergy Asthma Proc.* 2021; 42(Suppl 1):S11–S16.
20. Aksu K, Yesilkaya S, Topel M, et al. COVID-19 in a patient with severe asthma using mepolizumab. *Allergy Asthma Proc.* 2021; 42:e55–e57.
21. Frenkel LD, Gomez F, Bellanti JA. COVID-19 in children: pathogenesis and current status. *Allergy Asthma Proc.* 2021; 42:8–15.
22. Bellanti JA, Settipane RA. The challenge of COVID-19 that permeates the practice of allergy/immunology. *Allergy Asthma Proc.* 2021; 42:1–4.
23. Pitlick MM, Joshi AY. Considerations for asthma management and viral transmission in the era of COVID-19. *Allergy Asthma Proc.* 2021; 42:93–96.
24. Bellanti JA, Settipane RA. The war on infectious diseases: COVID-19 vaccines and the public: challenges and solutions. *Allergy Asthma Proc.* 2021; 42:5–7.
25. Perlini S, Ciprandi G, Castagnoli R, et al. Eosinopenia could be a relevant prognostic biomarker in patients with coronavirus disease 2019. *Allergy Asthma Proc.* 2020; 41:e80–e82.
26. Bellanti JA. The role of the allergist/immunologist in the COVID-19 pandemic: a Janus-faced presentation. *Allergy Asthma Proc.* 2020; 41:397–412.
27. Joshi AY, Mullakary RM, Iyer VN. Successful treatment of coronavirus disease 2019 in a patient with asthma. *Allergy Asthma Proc.* 2020; 41:296–300.
28. Larenas-Linnemann DE, Ortega-Martell JA, Blandón-Vijil MV, et al. Coronavirus disease 2019, allergic diseases, and allergen immunotherapy: possible favorable mechanisms of interaction. *Allergy Asthma Proc.* 2021; 42:187–197.
29. Kolinsky NC, Lockey RF. Chlorhexidine: an important cause of perioperative anaphylaxis. *Allergy Asthma Proc.* 2021; 42:257–259. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.