

COVID-19: A continuing challenge for the allergist/immunologist

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Coronavirus disease 2019 (COVID-19) has been a recurrent theme in past issues of the *Proceedings* and continues to be a hot topic for the allergist/immunologist.^{1–9} Because of the interest in the potential effect of COVID-19 on patients with allergic disease, the effects of COVID-19 on the clinical expressions of asthma, chronic urticaria, and allergic rhinitis are addressed in this issue. Although viral respiratory infections are recognized as the most common exacerbators of asthma, there has been increasing reports that asthma may not be a risk factor for worsening outcomes of COVID-19. In an effort to further clarify this issue, Sitek et al¹⁰ performed a comprehensive database search for studies evaluating outcomes among patients with COVID-19 and underlying asthma. Their meta-analysis included 16 observational studies comprising 92,275 patients. They report that among patients with COVID-19, asthma did not appear to significantly increase risk of hospitalization, length of hospitalization, ICU admission or death. Because of the importance of this reassuring information to patients, it was chosen as the basis for this issue's "For the Patient" section entitled "Outcomes among patients with COVID-19 and asthma." 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.

Transitioning from the effect of COVID-19 on asthma to the effects of COVID-19 on patients with chronic urticaria, Beyaz et al¹¹ addressed the psychological burden of COVID-19 on mild and moderate chronic spontaneous urticaria by prospectively evaluating 509 mild/moderate patients with chronic urticaria. The authors report that fear of COVID-19, anxiety, depression and stress during the COVID-19 pandemic, especially when strict isolation measures are taken, have a significant impact on mental health and urticaria activity in patients with mild/moderate chronic spontaneous urticaria.

Shifting from chronic urticaria to allergic rhinitis, Winders et al¹² analyzed the results of a preCOVID-19

national health care provider and patient survey of treatments for nasal allergies which was performed in November-December 2019. This corresponds to a time period after shared decision-making (SD) tools for sublingual immunotherapy (SLIT)-tablets and allergy immunotherapy (AIT) had become available. The objective of this analytic study was to compare survey results with previously reported surveys and to provide insight into the use of SLIT-tablets and AIT SD tools. Adults (N = 510) diagnosed with nasal allergies and health care providers (N = 304) treating patients with nasal allergies completed surveys involving nasal allergy management. Results showed not only that patients with nasal allergies continued to report inadequate symptom control and impaired activity, but also an underutilization of SLIT-tablets and AIT SD tool. The authors speculate that although social distancing due to COVID-19 may have negatively impacted SCIT administration, the increased use of telemedicine could have provided a possible advantage for at-home self-administration of SLIT-tablets.

Continuing with the theme of immunotherapy are reports from Werner and Bosso¹³ on the topic of intralymphatic immunotherapy for allergic rhinitis and Endo et al¹⁴ on the topic of long-term oral administration of transgenic rice containing cedar pollen T-cell epitopes for cedar pollen seasonal allergic rhinitis. The study by Werner and Bosso¹³ was a systematic review and meta-analysis of intralymphatic immunotherapy that demonstrated it to be a safe procedure capable of conferring desensitization to seasonal and nonseasonal allergens and alleviating allergic rhinitis symptoms, and reducing medication use. The report by Endo et al¹⁴ was the results of a randomized, double-blind, placebo-controlled study designed to examine the clinical efficacy of low-dose intake of transgenic rice administered for two successive seasons. They found that administration of transgenic rice significantly reduced allergen-specific T-cell responses and improved medication scores and rhinitis quality of life scores in the second season of administration.

Hereditary angioedema (HAE) has been the focus of two recent supplemental issues to the *Proceedings*.^{15–31} The current issue continues this focus, featuring three

papers that address HAE-related issues. Manning and Kashkin³² reviewed the phase II and III studies of berotralstat (BCX7353), a novel, oral prophylactic treatment for HAE. Berotralstat is a small molecule plasma kallikrein inhibitor taken once daily for the prevention of HAE attacks in patients aged ≥ 12 years. Study results demonstrated the efficacy of berotralstat as a long-term prophylactic agent for patients with HAE, showing a reduction in attack rate and on-demand medication usage. Berotralstat was well tolerated; and gastrointestinal treatment-emergent adverse events were generally mild and self-limited. Johnson et al³³ conducted a multi-center mixed retrospective/prospective study to determine the etiology and predictors of cluster attacks of HAE that recur despite pharmaceutical treatment. The authors analyzed all data acquired from all documented attacks in their HAE patient collective ($n = 132$) between 2015 and 2018. They found that repeat attacks were strongly associated with external triggers. The percentage of patients who had attacks as a result of exogenous triggers was higher in the cluster-attack group compared to the general HAE population. Patients receiving prophylactic treatment who experienced cluster attacks were highly likely to have been underdosing, which may explain the repeated attacks despite treatment. The authors recommend that in patients prone to cluster attacks, prophylaxis should be considered. Utilizing a questionnaire, Ocaik et al³⁴ AAP001-21R prospectively compared the health-related quality of life in children with HAE to patients with histaminergic angioedema. The study included 59 children with HAE, 60 children with histaminergic angioedema and 72 healthy controls. Results showed that HAE causes significant impairment of the health-related quality of life of children and their families. Although the quality of life of HAE patients were more negatively affected than was observed among histaminergic angioedema patients, histaminergic angioedema was shown to affect the quality of life as well.

Two articles in this issue address food allergy-related topics. In the first, Meadows et al³⁵ studied health care resource utilization associated with "allergen avoidance" as the sole form of peanut allergy management among commercially insured individuals. By analyzing a large US administrative claims database (1999–2017), they were able to determine that individuals with peanut allergy, managed solely with allergen avoidance, had significantly greater health care resource utilization that varied across all age groups, with more peanut allergy-related outpatient visits during preschool/school age and peanut allergy-related urgent care visits than among adults. Additionally, they were able to identify higher risk of peanut reactions resulting in inpatient and emergency department visits among individuals with previous peanut

reaction(s), asthma, and male sex. In the second food allergy article, Ocaik et al³⁶ report on their experience performing a total of 160 oral food challenges in 59 children suspected of having food protein-induced enterocolitis syndrome.

Component resolved diagnostic testing has been of clinical utility in the field of food allergy, but its role in other allergic diseases requires further exploration. In this issue, Engin et al³⁷ report on their evaluation of the potential contribution of component resolved diagnostics in diagnosis of Hymenoptera venom allergy. Study subjects consisted of 93 patients from 4 different centers in Turkey. Testing included prick and intradermal skin tests with commercial venom extracts, serum specific IgE (sIgE) levels for whole venoms, and sIgE analysis for venom allergen components by immunoblotting. The authors conclude that component resolved diagnostic testing seems to be more helpful in diagnosing vespid venom allergy than bee venom allergy, and that it can also help discriminate clinically significant sensitizations from irrelevant ones

Long-term studies in pediatric asthma provide valuable insights regarding the potential effect of asthma therapy on lung function. Unfortunately, airway remodeling has been repeatedly shown to be persistent in pediatric asthma patients despite treatment with controller medications. To provide further insight, Kwong et al³⁸ performed a retrospective study using a cohort of inner-city asthmatic children treated by an asthma specific disease management system (Breathmobile). In this issue, they report that airflow obstruction at time of first visit was significantly associated with poor lung functions in later life despite guideline-based asthma care. They conclude that current asthma therapy may not affect pathways leading to airway remodeling in asthmatic children.

There is a growing public interest in the potential long-term effects of exposure to phthalates, especially those that get into our food supply through packaging and food handling equipment. Although the association between prenatal exposure to phthalate and childhood atopic dermatitis has been previously investigated, the results have been inconsistent. In this issue, Jung et al³⁹ further explore the association between prenatal exposure to phthalate and childhood atopic dermatitis by performing a systematic literature review and meta-analysis. Their findings suggest that prenatal exposure to phthalates may be associated with the development of childhood atopic dermatitis.

This issue's Patient-Oriented Problem Solving (POPS) case presentation explores the differential diagnosis of a persistent urticarial rash in a newborn. 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 US 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, Dziewa et al⁴⁰ from the Division of Allergy and Immunology, Department of Medicine, Penn State College of Medicine (Hershey, Pennsylvania) lead the reader through this learning process, illustrating the complexity of the differential diagnostic process for this clinical presentation and the importance of a detailed history, physical exam, and appropriate laboratory assessment in arriving at a correct diagnosis.

In summary, the collection of articles found within the pages of this issue provides further insight into the intersecting crossroads of inflammation and disease which manifest as allergic, immunologic and respiratory disorders afflicting patients whom the allergist-immunologist serves. In particular, they exemplify how the complexities of COVID-19, allergen immunotherapy, hereditary angioedema, food allergy, asthma, and atopic dermatitis continue to challenge the allergist-immunologist. In keeping with the overall mission of the *Proceedings*, which is to distribute timely information regarding 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*.

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