

Evaluation and management of adverse reactions to the COVID-2019 vaccines

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Recent advances in the development of vaccines directed against the severe acute respiratory syndrome coronavirus 2 virus have revealed a need for a better understanding of the evaluation and management of both immediate and delayed vaccine-induced cutaneous hypersensitivity reactions to these new immunizing agents.¹ This issue of the *Proceedings* includes four articles that address this need, beginning with a report by Aquino *et al.*,² who performed a literature review focused on delayed reactions to vaccines, including possible causative agents and practical information on how best to diagnose, evaluate, and manage subsequent dose administration of these vaccines. The authors suggest that evaluation by patch testing can sometimes be helpful to identify the causative role of excipient components variably found within vaccines, such as antibiotics, formaldehyde, thimerosal, and aluminum. Further, they conclude that, in most cases, delayed cutaneous reactions are not contraindications to further vaccine administration.

In continuing with the problem of delayed vaccine-induced cutaneous hypersensitivity reactions, Pitlick *et al.*³ report on a retrospective case series study of 12 patients who were referred to the Mayo Clinics for evaluation of delayed systemic urticarial reactions after messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccination. The authors conclude that reactions of this type are not life-threatening, can be treated with antihistamines, and are not predicted by vaccine excipient skin testing. They suggest, further, that although these reactions are not a contraindication to subsequent vaccination, patients should be counseled with regard to the possibility of their recurrence after succeeding vaccine doses.

Although urticaria has been reported after mRNA COVID-19 vaccination, it is unclear if mRNA vaccination against severe acute respiratory syndrome coronavirus 2 can trigger new cases of chronic spontaneous urticaria (CSU) or relapse of CSU after

long-term remission. To help elucidate this issue, Magen *et al.*⁴ provide a retrospective report on 32 clinical cases of patients with new-onset CSU and 27 cases of CSU in remission that relapsed within 3 months after BNT162b2 mRNA (Pfizer-BioNTech) vaccination. The authors report that the relapsed CSU and new-onset CSU groups had more allergic comorbidities overall than a CSU control group and a healthy control group. Although their study was not designed to determine causation, the authors speculate that it is possible that BNT162b2 mRNA vaccination serves as a provoking and/or relapsing factor of CSU in individuals with allergic diseases and/or a predisposition for autoimmunity.

Finally, some much-needed guidance with regard to the management of second-dose COVID-19 mRNA vaccine administration for people with adverse reactions after the first dose is provided by a study by Gallagher *et al.*⁵ These authors used a protocol of premedications that allowed health-care personnel to safely receive their second mRNA COVID-19 vaccine dose. The advantages of their protocol is that it is adaptable and can be used in settings in which an allergy/immunology referral is not immediately available.

The next group of articles focuses on issues associated with allergic disease(s) in children that include the changing epidemiology of respiratory allergies and eczema, incidence of food allergy, clinical features of anaphylaxis, and prognosis of food-induced anaphylaxis (FIA) in schoolchildren populations. In analyzing data from four consecutive surveys performed in Patras, Greece, since 1991, Malliori *et al.*⁶ report that, although the prevalence of asthma and rhinoconjunctivitis declined during the past decade in Greek schoolchildren, the prevalence of eczema continued to rise. In analyzing data on the incidence of food allergy in Olmsted County, Minnesota, Almodallal *et al.*⁷ report a steady increased incidence from 2002 to 2008, that remained relatively stable between the years 2008 and 2013, and again presented a rising trend over the next 5 years until 2018. The authors suggest that further

investigations are necessary to determine the potential dietary changes and other factors that may be causally associated with these epidemiologic trends. When shifting back to an international perspective, Serbes *et al.*⁸ report on the clinical features of anaphylaxis in Turkish children. Medical records of 147 children diagnosed with anaphylactic reactions to a variety of allergenic agents were retrospectively analyzed. The overall leading cause of anaphylaxis was found to be foods, followed by drugs and bee venom. Overall, fewer than half of the patients were administered epinephrine in the emergency department, and only 27.3% were referred to an allergy specialist. Inadequate treatment was most evident in infants and patients with FIA. Children with drug-induced anaphylaxis had the highest rate of severe anaphylaxis. The authors conclude that there is a need to improve anaphylaxis recognition and management in all children regardless of age and trigger.

Another group of investigators in Turkey, Buyuk Yaytokgil *et al.*,⁹ performed a study to evaluate the natural history of FIA in children and determine the factors that affect prognosis. In analyzing data from 185 children with FIA who were followed up for at least 3 years, the authors report that approximately a third of patients with FIA developed tolerance within 3 years. The authors conclude that regular follow-up and reevaluation of tolerance status is necessary to avoid unnecessarily prolonged dietary restrictions. Because of the importance of this information to patients who suffer from this condition, it was chosen as the basis for this issue's "For the Patient" section entitled "Food Allergies Can Resolve Over Time." 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 shifting focus to hereditary angioedema (HAE), a frequent publication topic for the *Proceedings*,¹⁰⁻³⁷ in a report by Radojicic,³⁸ the most recently updated HAE guidelines are reviewed, together with the key points and real-world feasibility of their incorporation into clinical practice. In addition to the main points consistent with the HAE guidelines, the author provides useful recommendations for evaluation and classification of HAE as well as evidence-based strategies for treatment. However, she wisely recommends that future attention be focused on the evaluation and continuous assessment of the burden of illness and quality of life.

The provision of health care globally and the burden of illness attributable to HAE has been further exacerbated by the disruptive effects of the COVID-19 pandemic.²⁸ Online global surveys were conducted in a report by Grivcheva-Panovska *et al.*³⁹ that evaluated patient and health-care professional perspectives on

the global impact of COVID-19 on HAE medical care. Both patients and health-care professionals reported that the pandemic limited the availability of HAE medical care. Survey results also showed that, although telehealth use has increased across the globe, it has been more successfully implemented in high-income countries, which thus leads the authors to conclude that disparities in medical care and technological infrastructure may exacerbate these challenges in non-high-income countries.

This issue of the *Proceedings* includes two articles with juxtaposing perspectives on the management of eosinophilic esophagitis (EoE), one from authors at a multidisciplinary esophagitis clinic and the other from a non-tertiary-care, private practice perspective. In an original article, McMurry *et al.*,⁴⁰ representing the perspective of a multidisciplinary clinic at the Walter Reed National Military Medical Center, the clinical and histologic outcomes of patients with EoE were assessed by conducting an observational, retrospective chart review. Management in the multidisciplinary clinic was associated with a reduction in solid dysphagia by 70.9%, poor growth by 70.8%, and emesis or regurgitation by 87.5%. The authors observed that 48.5% and 62.1% had histologic remission on the initial and any post-multidisciplinary endoscopy, respectively. Although an observational study, these findings seem to suggest that the management of patients with EoE in a multidisciplinary clinic may improve the likelihood of clinical and histologic remission. Yousef *et al.*⁴¹ provide a review article that concentrates on a step-wise approach for the allergist working in non-tertiary-care private practice. The authors performed a medical literature search from which they distill for the allergist, practical aspects with regard to the latest developments in the diagnosis and management of EoE.

Three additional topics addressed in this issue focus on issues associated with intranasal corticosteroids (INCS) safety, asthma control, and penicillin allergy. Although INCS are considered the cornerstone of treatment for chronic rhinosinusitis and are generally considered safe, there is some concern that chronic use may lead to ocular adverse effects, such as increased intraocular pressure. To assess ocular safety of the exhalation delivery system (EDS) with fluticasone propionate in patients with chronic rhinosinusitis with nasal polyps, Skoner *et al.*⁴² collected ocular safety data during two randomized, double-blind, placebo controlled studies with open-label extensions. They report that no increased risk of elevated intraocular pressure was detected with EDS-fluticasone propionate; the rate of cataract development was similar to EDS-placebo and to that reported with other INCS.

In transitioning to the topic of asthma control, Ganti *et al.*⁴³ report on the effect of socioeconomic status on

the measurement of asthma control, which has generally been found to be worse among the economically disadvantaged. These authors studied whether the Asthma Control Test (ACT) (QualityMetric, Johnston, RI) is affected by socioeconomic status as evaluated by percentage of the federal poverty level and education level. The authors report finding a positive correlation of improved mean score on the ACT ($p < 0.001$) with higher education status and higher federal poverty level status. They conclude that socioeconomic status plays a factor in the way patients perceive their asthma control and how they relate to the ACT.

Most patients who report penicillin allergy are found to tolerate penicillin later in life. Harada *et al.*⁴⁴ performed a study to better understand patient perspectives on penicillin allergy testing. The authors surveyed 88 patients with documentation of penicillin allergy with regard to their reaction history and knowledge and/or perspectives about penicillin allergy and testing. The authors report that fewer than half of participants (45.5%) who had penicillin allergy reported awareness that testing for penicillin allergy was available. Awareness of penicillin allergy testing was significantly associated with completion of testing. Fear about adverse effects from testing was the most reported barrier. The authors emphasize the importance of increasing awareness of the availability and safety of penicillin testing through patient education and collaboration with other specialties.

In summary, the collection of articles found within the pages of this issue provides further insight into the intersecting crossroads of inflammation and disease that manifest as allergic, immunologic, and respiratory disorders that afflict patients whom the allergist/immunologist serves. In particular, they exemplify how the complexities of COVID-19, vaccination, HAE, allergic diseases in childhood rhinitis, food allergy, EoE, anaphylaxis, asthma control, chronic rhinosinusitis with nasal polyps, 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*.

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