

Stress, cytokines, depression, bone fractures, and asthma

Asthma is a major cause of global health problems and affects >300 million individuals throughout the world. An expanding body of evidence has shown that osteoporosis and depression, compounded by stress, are important comorbidities. Traditionally, their coexistence has been attributed to causality or to independent processes. However, an increasing number of epidemiologic and basic molecular studies have provided support for a correlation among bone, the neurologic system, and the lung that suggests that shared pathways, cells, cytokines, and mediators bring these entities together.

Four articles in this issue focus on various associations with asthma, ranging from bone health to depression, genetics, and vitamin D₃. In the first article, Shaheen and Silverberg¹ sought to determine whether asthma is associated with osteopenia, osteoporosis, osteomalacia, and fractures in U.S. adults. They performed a cross-sectional study of >198 million children and adults, including >10 million with asthma from the 2006–2012 National Emergency Department Sample, which represents a 20% sample of emergency department visits throughout the United States. They found that emergency department visits with the diagnosis of asthma were associated with significantly higher odds ratios for osteopenia, osteoporosis, osteomalacia, and pathologic fractures.¹ In addition, patients with asthma and with long-term steroid use had higher odds of these conditions compared with patients with asthma and without long-term steroid use.¹

Depression is another complication of asthma that can be associated with high morbidity, which affects disease control and quality life. Wufuer *et al.*² studied the incidence of depression and its influencing factors in 387 patients, from Xinjiang, China, with asthma. Logistic regression analysis indicated that the severity of asthma symptoms, taking asthma medication, the frequency of asthma attacks, lack of education, and Uighur ethnicity were the major risk factors for depression in this population of patients with asthma.²

The relationship of genetics and asthma is yet another mystery of asthma that requires continued investigation. In this issue, Bisuyuk *et al.*³ reported the results of their genetic studies of the association of CD14 C159T and TLR4 Asp299Gly polymorphisms, with various phenotypes of asthma in 331 adult

patients from Crimea, Ukraine. They found that TLR4 Asp299Gly polymorphisms were associated with asthma and with decreased odds of non-atopic asthma compared with atopic asthma but that there was no association with CD14 C159T polymorphisms.³

The association of vitamin D₃ status and asthma pathogenesis continues to be of great interest.^{4,5} In this issue, Mohammadadeh *et al.*⁶ reported on their case-control study of the association of serum 25-OH vitamin D₃ with serum immunoglobulin E (IgE) and the Pediatric Asthma Severity score in 100 pediatric patients with asthma. In comparison with a control group that consisted of 100 sex- and age-matched healthy blood donors, vitamin D₃ deficiency was found to be associated with the severity of exacerbations and serum IgE levels in the pediatric asthma group.⁶ The authors concluded that vitamin D₃ deficiency can have an important role in pediatric asthma pathogenesis, possibly through IgE.⁶

Three articles in this issue focused on drug hypersensitivity, ranging from antibiotics to aspirin (ASA) and to proton-pump inhibitors (PPI). In the first article, Khan⁷ provides a review of the history of the discovery of penicillin, implications of the penicillin allergy label, and various de-labeling strategies as well as a brief overview of the approach to cephalosporin, fluoroquinolone, and macrolide allergies. In the second article, Orgeron *et al.*⁸ provide original research on the prevalence and management of ASA hypersensitivity in a cardiology practice. The authors conducted an electronic medical record review of 11,375 individuals, 5052 (44%) in the ambulatory setting, and 6323 (56%) admitted for percutaneous coronary intervention. The prevalence of ASA hypersensitivity was found to be 1.88% ($n = 214$), and 69 (32.2%) were mistakenly labeled as “allergic” for manifesting only gastrointestinal symptoms.⁸ Of the 214 patients who had documented ASA hypersensitivity, 108 individuals (50.46%) had coronary artery disease.⁸ The authors concluded that ASA hypersensitivity is often not documented correctly, is misdiagnosed, or is not appropriately managed.⁸ Their results demonstrate a need for improved management of ASA hypersensitivity, including appropriate referral for ASA desensitization and for combating unnecessary avoidance in patients with intolerance due to expected adverse effects.

In the third drug hypersensitivity article, Ozdemir and Bavbek⁹ performed a literature review on hypersensitivity reactions to PPIs. They report anaphylaxis

to be the most common clinical presentation in patients with immediate hypersensitivity reactions to PPIs, followed by urticaria and/or angioedema, and a variety of other cutaneous adverse reactions.⁹ The authors concluded that a causal relationship exists between hypersensitivity reactions and PPIs but caution that variability in the cross-reactivity patterns among PPIs does not permit a clear mechanistic understanding.⁹ Because of the importance of this article and its clinically useful implications, it was chosen for this issue's "For the Patient" section. 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.

Two articles in this issue address the importance of safety issues with regard to therapeutics. In the first article, Simon *et al.*¹⁰ reviewed the manufacturing process for plasma-derived C1-inhibitor (C1-INH) replacement therapy in patients with hereditary angioedema, a disease state that has frequently been addressed in recent issues of the *Proceedings*.^{11–21} They provide a comprehensive overview of the procedures used in donor screening, donation and manufacturing pool testing, manufacturing, and pharmacovigilance, which ensure that plasma-derived C1-INH products have the safety, quality, identity, potency, and purity that is necessary to provide the intended therapeutic effect. In the second article, Bernstein and Epstein²² reviewed strategies to minimize adverse reactions to allergen immunotherapy, with a focus on the lessons learned from the American College of Allergy, Asthma & Immunology/American Academy of Allergy, Asthma & Immunology National Surveillance Study of Adverse Reactions to Allergen Immunotherapy (2008–2017). They reported that data from annual surveys identified the following risk factors for systemic reactions: history of systemic reactions to subcutaneous immunotherapy, administering injections in patients with uncontrolled asthma, use of accelerated build-up regimens, and never adjusting doses during the height of the allergy season.²² They also reviewed the safety profile of sublingual immunotherapy, which is notable for no fatal reactions having yet been reported for either sublingual tablet or liquid formulations.²² They concluded that risk management should mainly focus on patients with uncontrolled asthma by withholding injections in such patients with recent worsening in asthma symptoms and lung function.²² Finally, because nearly all fatal and systemic reactions occurred within 30 minutes of injections, a 30-minute observation period is recommended.

The classification and understanding of the pathophysiology of mast cell activation syndrome (MCAS) remains a confusing topic for many allergists. In this issue, Khalid and Lieberman²³ fill this unmet edu-

cational need by clarifying our understanding of MCAS, its diagnostic tests, and management strategies. They provide a review of the consensus diagnostic criteria as well as the classification into primary MCAS (clonal mast cell disorders or mastocytosis), secondary MCAS (non-clonal mast cell disorders associated with atopy, inflammation, other processes), and idiopathic MCAS (diagnosis of exclusion).

Telemedicine is a rapidly growing platform for the provision of medical care; however, many allergy/immunology practitioners are undecided with regard to engaging with patients on this platform. In this issue, Waller *et al.*²⁴ reviewed the benefits and risks of incorporating virtual visits into an allergy/immunology practice. They concluded that allergists need to familiarize themselves with this new technology because the convenience of telemedicine will certainly drive patients to demand it.²⁴

This issue's Patient-Oriented Problem Solving (POPS) case presentation explores the differential diagnosis of a late-preterm infant with lymphopenia detected via an abnormal newborn screen. 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, Lutfeali *et al.*,²⁵ from the University of Texas Southwestern Medical Center, 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 examination, 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 genetics and environment, which manifest as the allergic, cutaneous, and respiratory disorders that afflict patients served by the allergist/immunologist. In particular, they exemplify how the complexities of asthma, allergic rhinitis, drug hypersensitivity, hereditary angioedema, and mast cell disorders 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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