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Perspective

Increasing our knowledge base of asthma

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Introduction

During the past decade, there has been an explosion in our knowledge of asthma. There are new descriptions of phenotypes, endotypes, and even genotypes. New approaches to management have been and continue to be developed. The realization and characterization of a spectrum of overlap with chronic obstructive pulmonary disease (COPD) in many patients with asthma have been reported in detail and approaches to management of patients with severe asthma continue on the forefront. These and other aspects of asthma are well represented in the more than 200 articles published on asthma since 2015 in the *Annals of Allergy, Asthma and Immunology*. Through the content of these *Annals* articles, clinicians who care for these patients can have a better understanding of the epidemiology, optimization of control measures, and therapy available to effectively treat this illness. In this article we highlight some gains in our understanding of asthma through *Annals* publications. The intent is to provide a synopsis in a single article that will allow the reader to refer to specific *Annals* publications for further information.

Epidemiology

The epidemiology of asthma is important to understand in identifying factors that influence the risk of developing the disease, issues related to management challenges, and identifying distinctive populations as candidates for specific therapeutic approaches. When considering factors to identify at-risk children, Yamamoto-Hanada et al[1] found that antibiotic use within the first 2 years of life was a risk factor for current asthma in 5-year-old children. Van Meel et al[2] explored the association between the duration and exclusiveness of breastfeeding and school-age lung function and asthma by comparing 2 to 4 months with longer duration and found that shorter duration and non-exclusivity of breastfeeding were associated with a lower forced expiratory volume in 1 second and forced vital capacity but not with asthma diagnosis at school age (10 years old). Through analysis of the Genes-environments and Admixture in Latino American (GALA II)[3] study and the Study of African-Americans, Asthma, Genes, and Environments (SAGE II),[4] Fishbein et al[5] demonstrated that pest allergen sensitization was associated with increased risk of asthma exacerbations in urban minority youth. Furthermore, Puerto Rican and other Latino youth sensitized to mouse allergens were more likely to have asthma-related hospitalizations than Mexican youth. Akin et al[6] found that the simple anthropometric measure of neck circumference was associated with asthma risk in obese children. Lapin et al[7] demonstrated that prenatal C-reactive protein levels were associated with asthma diagnosis by 3 years of age and wheezing in year 3 in a high-risk urban cohort of mostly Mexican children. They suggested that maternal systemic inflammation might reflect a prenatal environment that could increase offspring susceptibility to develop wheezing and asthma young in life.

Asthma Control

Control of symptoms, exacerbations, and associated morbidities is the fundamental goal of quality asthma care, yet it is clear that, depending on the stakeholder (patient, family, provider, or payer), the meaning of asthma control and how it is measured can vary. There were several articles that explored the issue of achieving and maintaining control and measures of control in asthma. Franklin et al[8] explored the Predictors of Emergency Department Utilization in Children with Persistent Asthma in an inner-city population and found, after adjustment for socioeconomic status,

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predictors of emergency department (ED) use in white children included an ED visit in the previous year and sensitization to pets and dust. In contrast, predictors for ED use in African-American children included ED use in the previous year, number of asthma controller medications, routine forced expiratory volume in 1 second less than 80% predicted, blood eosinophil count larger than 4%, and mold allergen sensitization.

Anderson et al[9] expanded the notion that ideal inhaled corticosteroid (ICS) titration might be dependent on other measurements beyond assessment of symptoms and spirometric results. They found that, although escalation of ICS dosing in persistent asthma led to improvement in pulmonary function and symptoms, a plateau was reached at low to medium doses (equivalent to 200–800 μg of beclomethasone dipropionate). Interestingly, however, ICS dose adjustment resulted in further improvement of inflammatory measurements without a plateau effect. Fractional exhaled nitric oxide (FeNO) values consistently decreased across all ICS dose increases without plateau ($P < .0001$), as did blood eosinophil counts ($P = .03$). Serum eosinophilic cationic protein concentrations decreased only at higher ICS doses ($P = .002$). Airway hyperreactivity (methacholine, histamine, and mannitol) also showed significant improvement across all doses without a plateau effect. An accompanying editorial by Kohn and Oppenheimer[10] reinforced the need for further indicators of asthma control beyond symptoms and spirometry. In addition, it reminds us that no one control measurement is perfect for all patients with asthma.

Building on this observation, a study by Chipps et al[11] explored the utility of various tools available to help patients (and families) manage short-term variability in asthma symptoms, focusing on when and how to implement a sustained step up in therapy. They proposed an "asthma yardstick," which is a comprehensive update on how to develop individualized step-up plans for asthma therapy in patients with less well-controlled or poorly controlled asthma.

Although a pilot study, Phillips et al[12] performed the first prospective cross-sectional study investigating the association between chronic rhinosinusitis symptoms and asthma control measures. They demonstrated a correlation between chronic rhinosinusitis symptom severity and asthma control in their study population. As they noted, further work is needed to determine whether a decrease in chronic rhinosinusitis severity can reliably translate to improvement in asthma control. A study by Sullivan et al[13] examined the association between asthma control cutoffs and longitudinal changes using the Asthma Control Questionnaire 5 (ACQ-5), with economic outcomes, and provided preliminary economic data on possible control cutoffs for the ACQ-5. Not surprising is that improved asthma control over time appeared to result in significant financial savings. These data provide a rationale for committing additional financial resources to improve control.

Arroyave et al[14] investigated whether differences in morbidity in patients with asthma occur based on their atopic status. They indeed found important differences in asthma morbidity, with those with atopy having more severe asthma. However, there was no difference in asthma control between participants with and without atopy as measured by the Asthma Control Test (ACT). FeNO was a significant marker of inflammation only in participants with atopy, whereas those with high total immunoglobulin E (tIgE) in the 2 groups had greater asthma severity and significantly higher FeNO. They suggested that tIgE could predict asthma severity and FeNO independent of atopic status.

Asthma Phenotypes

To provide better outcomes for patients with asthma, recent literature has focused on personalized medicine and phenotypic discriminators. There were several recent articles in the *Annals* that addressed this issue, including a review by Desai and Oppenheimer.[15] Recent literature has focused on stratifying asthma based on the airway inflammatory milieu. Most current measures have focused on FeNO and peripheral blood eosinophil counts in clinical practice with sputum and serum periostin assessments in the research setting.

Park et al[16] assessed the utility of serum progranulin levels as a phenotypic biomarker. Progranulin is a protein secreted from the airway epithelium that attenuates the downstream cascade of neutrophilic inflammation. They found that serum progranulin levels had a positive correlation with pulmonary function in patients with asthma and a negative correlation with blood neutrophil counts, with a lower serum progranulin level associated with severe asthma. They pointed out that, although the exact mechanism of progranulin's anti-inflammatory action has not been fully defined, it still could be useful as an indicator of severe asthma with airflow obstruction and that it might have an inhibitory role in neutrophilic airway inflammation.

To further examine phenotypic and endotypic differences in asthma, Tran et al[17] examined the overlap of atopic, eosinophilic, and T-helper cell type 2 high asthma phenotypes in the general population by mining data from the National Health and Nutrition Examination Survey (2005–2006) and found significant overlap among eosinophilic, atopic, and T-helper cell type 2 high asthma phenotypes in a general asthma population.

Beyond classification based on the relative contribution of T-helper cell type 2–based interleukin (IL)-4, IL-5, and IL-13 (so-called T2 high and low), there has been a great deal of discussion about a crossover between asthma and COPD, initially described as "asthma COPD overlap syndrome" and most recently as "asthma-COPD overlap" by the Global Initiative for Asthma.[18] A review by Desai et al[19] reinforced considering this a phenotype of the 2 illnesses when considering treatment options. A retrospective observational study by Liang et al[20] found that patients with COPD overlapping with bronchial asthma compared with COPD alone were more likely to be female ($P = .004$) and experienced more severe respiratory exacerbations ($P = .04$) despite being younger ($P = .008$). They also were more likely to have a family history of asthma ($P = .03$), have higher serum allergen-specific IgE ($P = .004$), and have a positive allergic history ($P = .003$). When trying to differentiate these 2 illnesses, Schwingel et al[21] found that sputum pentraxin 3 (a known neutrophil secretagogue) levels were increased in patients with COPD and had good power to discriminate patients with COPD from patients with asthma and healthy individuals.

Asthma Therapy

The articles published on asthma therapy (>100 since 2015) have been extensive. This article focuses on articles addressing adherence, safety, and new and emerging therapies. Lack of adherence in the use of controller therapy and inappropriate response to loss of asthma control are significant causes of clinical failure of clinical asthma interventions.[22] A study by Izadi and Tam[23] evaluated the real-world benefits of patient involvement with an allergist-immunologist and identified impediments for patients in establishing allergy subspecialty care. They found improvement in outcomes in patients who received allergy-immunology follow-up, particularly when the allergists could identify key barriers and prevent future nonadherence. Interestingly, even choosing to go to the ED could be a consequence of some of these barriers.

In a study of inner-city children, Mudd et al[24] performed a cluster analysis to correlate caregiver reasons for the decision to use the ED for asthma care as opposed to outpatient care. They identified 3 clusters for decision making: urgency, preference for use of the ED, and issues of access to care. The perception of urgency was the most common reason reported by caregivers (91%) followed by reporting a preference for the ED for care (37%) and reporting issues