



Year in review: asthma

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Introduction

The year 2014 was a busy one for the *Annals*, which featured an evolving literature on asthma. Several themes emerged, including characterization of phenotypes, biomarkers of inflammation, environmental factors, and treatment, particularly for severe asthma. Notable last year was the publication of an updated asthma practice parameter regarding yellow zone management.

The Yellow Zone Practice Parameter

The Yellow Zone Practice Parameter reviewed the evidence for home interventions for patients when they lose asthma control and enter the yellow zone in the “traffic light” model of asthma action plans.¹ As pointed out in the parameter, patients often adjust their medications (with or without the advice of their physician) when faced with loss of control but, unfortunately, often do so inappropriately. The hope of the parameter is to offer evidence-based recommendations for patient-directed treatment changes. It is meant to create a partnership between the provider and the patient, empower patients to manage their asthma symptoms, and prevent patients from entering the red zone. Strong recommendations in the parameter include instructing patients to activate the yellow zone intervention plan early on when there is acute loss of asthma control and/or at the onset of an upper respiratory infection if this is a known trigger. Beyond the recommendations made in the Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma of a short-acting β -agonist use in the yellow zone, the practice parameter poses other treatments as options, including symptom-driven use of an inhaled corticosteroid (ICS) with a concomitant β -agonist. The approach relies on “dynamic dosing,” which is the use of ICS with a reliever or “adjustable

maintenance dosing,” which entails combination therapy of a fast-acting ICS plus a long-acting β_2 -agonist driven by symptoms.

In the end, after an exhaustive review of the literature, the yellow zone workgroup concluded that there is a paucity of data regarding interventions in the yellow zone and called for further research about potential interventions during this tenuous state of lost asthma control.

Biomarkers of Inflammation

During the past year, there has been significant interest in the usefulness of existing biomarkers and the emergence of novel noninvasive biomarkers of inflammation to identify specific phenotypes, provide early objective evidence of lost asthma control, and assess treatment response.

Exhaled Nitric Oxide

In a letter in the *Annals*, Chipps et al² discussed the findings of a small-scale observational study conducted over a 6-month period to characterize patients presenting with fractional exhaled nitric oxide (FeNO) levels higher than 100 ppm. Of the 40 patients in their study, they identified a group of patients who had normal spirometric findings and asthma control test scores, all of whom were naive to steroid use or taking a low dose of ICS. The investigators hypothesized that this group, with apparently normal lung function despite very high FeNO levels, could represent a previously uncharacterized population vulnerable to exacerbations of their asthma. An accompanying editorial by Desai and Marshall³ discussed the findings of this article and the article by LaForce et al,⁴ which looked at the impact of FeNO measurements on clinical decisions with regard to medication titration. Desai and Marshall concluded that significant gaps in our knowledge of the optimal use of FeNO exist, further robust research in this area is needed, and the expectation of a perfect biomarker could in fact be unrealistic.

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Blood Eosinophil Counts

Sputum eosinophil counts correlate well with airway inflammation. However, they are cumbersome to obtain and are not practical for routine outpatient asthma care. With this in mind, Tran et al⁵ examined blood eosinophil counts, which are low cost and widely available, and their correlation with self-reported asthma attacks. Using National Health and Nutrition Examination Survey (NHANES) data from 2001 to 2010 on 3,162 patients with asthma and available blood eosinophil data, they found that children with asthma and higher blood eosinophil counts appeared to report more frequent asthma attacks in the previous year than those with lower eosinophil counts. This association was suggested but less clear for adults with asthma in this study.

The literature is always being updated on the optimal use of currently available biomarkers and the applicability of emerging noninvasive inflammometry tools. We expect this trend will continue in 2015, because there is great interest and need among practicing allergists to identify clinical deterioration early with objective noninvasive measurements, identify asthma phenotypes and high-risk patients, and monitor response to tailored therapy.

Environmental Exposures

Pesticide Exposure

In 2014 the *Annals* also featured an article by Jerschow et al⁶ that examined the association between urine levels of dichlorophenols and asthma morbidity in patients with wheezing and atopy and those with wheezing and without atopy. Dichlorophenols are organochlorine pesticides that are found in contaminated water, air, and pesticide-treated crops. Previous reports have suggested that organochlorine compounds might have an immune modulatory effect and lead to increased incidences of atopic diseases in children and adults by currently unknown mechanisms.⁶ The investigators extracted data for 2,125 participants from the NHANES 2005 to 2006 data in a retrospective review and found that patients with atopy and wheezing with higher levels of urinary dichlorophenol showed statistically significant higher rates of asthma morbidity. Patients with atopy and wheezing and higher 2,5-dichlorophenol levels were more frequently diagnosed with asthma (odds ratio [OR] 4.7, $P < .001$), required more asthma medications (OR 2.2, $P < .046$), and reported more exercise-induced wheezing (OR 5.8, $P < .045$) than those with low levels. No such association between asthma morbidity and urinary dichlorophenol levels was found in patients without atopy and with wheezing. However, the investigators did not find any correlation between 2,4-dichlorophenol, a byproduct of triclosan, and triclosan levels.

Chemical Exposures

A letter published in the *Annals* by Savage et al⁷ looked more closely at asthma control and triclosan levels, which is a broad-spectrum antimicrobial chemical found in personal care products such as toothpaste and hand soap. Data in the study were similarly obtained from the 2005 to 2010 NHANES. The investigators found that in 639 patients with asthma and available triclosan levels, the likelihood of reporting an asthma “attack” in the previous year increased with increasing urinary triclosan levels (adjusted OR 1.79, $P = .05$, in the third tertile of urinary triclosan). The relation between measurements of urinary dichlorophenol and triclosan levels and asthma control remains to be seen.

Beyond markers of environmental exposures, contributors to the *Annals* during the past year have explored the mechanisms, prevalence, and diagnosis of occupational exposures in patients with asthma. Exposure to hop dust, which comes from the hop plant harvested principally for brewing beer, was presented as a potential causative agent in occupational asthma. In a study

conducted using Washington State compensation claims, Reeb-Whitaker and Bonauto⁸ found that the incidence rate of respiratory disease in hop workers was 30 times (15 cases per 10,000) greater than in a comparison group of agricultural workers. Pham et al⁹ conducted a mechanistic study of toluene diisocyanate, a chemical implicated in occupational asthma. They found that toluene diisocyanate in the workplace binds to tissue transglutaminase to form a conjugate that can induce serum immunoglobulin production and subsequent airway inflammation and remodeling in patients with occupational asthma from toluene diisocyanate exposure.

Special Considerations in Specific Populations

Asthma in the Elderly

The process of aging translates to structural and functional changes in the respiratory system, but this has not been well characterized. Inoue et al¹⁰ attempted to characterize the physiologic, radiologic, and immunologic features of elderly asthma in a retrospective study of elderly (>65 years old, $n = 45$) and nonelderly ($n = 67$) patients with asthma using multiple diagnostic measurements. They found that elderly patients with asthma had significantly lower spirometric measurements for forced expiratory volume in 1 second, forced expiratory flow of 25% to 75%, and ratio of forced expiratory volume in 1 second to force vital capacity and significantly greater airway wall thickening and air trapping by computed tomographic measurements. Also, impulse oscillometry indicated that elderly patients with asthma showed greater total airway resistance and measurements suggesting greater involvement of small airway disease compared with nonelderly patients. Interestingly, there was no differences observed in blood or sputum cell counts, FeNO measurements, and methacholine airway responsiveness between the 2 groups, but the elderly group was less likely than their younger counterparts to have atopy.

Drug Therapies

Severe Asthma

Treatment with omalizumab in allergic asthma has been shown to significantly decrease asthma exacerbations and medication use and improve quality-of-life scores and spirometric indices. Tajiri et al¹¹ sought to further elucidate the effects of omalizumab by studying its impact on the small airways and airway remodeling, in addition to its effect on the large airways. They conducted a prospective, single-arm study of 31 adult patients with severe refractory asthma despite high-dose ICS and assessed numerous clinical variables at baseline and after 16 and 48 weeks of treatment. For the 26 patients who completed 48 weeks of treatment, the investigators noted decreases in FeNO and sputum eosinophilia and improved peak expiratory flow rate and symptom scores. In addition, they found decreases in alveolar NO levels and airway wall thickness as assessed by computed tomography at 48 weeks, thereby purporting an effect of omalizumab treatment on decreasing small airway inflammation and reversing airway remodeling. An accompanying editorial by Lavietes¹² highlighted that subjective improvement in the study was not accompanied by functional improvement in lung function testing, and that relying on peak expiratory flow rate is questionable because it is an effort-dependent measurement.

Beyond benefits in allergic asthma, there exists a body of literature regarding the use of omalizumab in other respiratory diseases. Bonini and Paggiaro¹³ reviewed the evidence from trials and case reports regarding the use of omalizumab in allergic rhinitis, nonallergic asthma, nasal polyposis, allergic bronchopulmonary aspergillosis, and allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. This publication examined fairly robust evidence from clinical trials for the clinical benefits of omalizumab

in allergic rhinitis and discussed numerous case studies that showed steroid-sparing effects in patients with allergic bronchopulmonary aspergillosis with or without cystic fibrosis.

Some studies also attempted to better characterize airway inflammation in an effort to identify potential novel targets for biologics. After examining the lung tissue of 12 nonsmokers with fatal asthma, Oda et al¹⁴ found increased numbers of lymphocytes, eosinophils, interleukin-18 (IL-18) protein, IL-18 receptor, and CD8⁺ T cells in the lungs of patients with fatal asthma compared with those of patients with mild asthma. An accompanying editorial by Traister and Wenzel¹⁵ remarked that the link between IL-18 and asthma remains unclear, as does the role of CD8⁺ T cells in asthma. They called for further mechanistic studies using animal models and human in vitro systems to further elucidate the role of the IL-18 pathway. Depending on these findings, the IL-18 pathway could be a potential target for the development of new biologics.

Acute Asthma

Rodrigo and Castro-Rodriguez¹⁶ conducted a meta-analysis of 11 clinical trials including 697 participants to examine the efficacy of heliox in the treatment of acute asthma. Patients receiving heliox had a 17.2% increase in mean change from baseline peak expiratory flow compared with patients receiving oxygen alone ($P = .005$). Patients with severe and very severe asthma showed a better response. Of importance, the use of heliox significantly decreased the rate of hospitalization (OR 0.49, $P = .003$). An accompanying editorial by Oppenheimer and Desai¹⁷ remarked that this study provides reassuring data to support the use of heliox in powering β -agonist nebulization in cases of moderate to severe asthma in the emergency department (ED), but that larger studies with optimized heliox delivery systems and outcome measurements are needed. The editorial also pointed out that treating severe asthma and other conditions in the inpatient setting can ensure stability and longevity for the field of allergy in an otherwise shifting health care field.

Another publication this past year by Doymaz et al¹⁸ examined the use of continuous intravenous terbutaline in pediatric patients arriving to the ED with severe asthma. They conducted a retrospective chart review and compared outcomes in patients transferred from an outside hospital ED with late start of terbutaline ($n = 35$) with those in patients presenting to the investigators' ED with early initiation of intravenous terbutaline ($n = 85$). Patients from outlying hospital EDs had delayed and thus shorter acute-care duration of intravenous terbutaline, with resultant 60% respiratory failure requiring mechanical ventilation vs 16% from the early start group in the investigators' ED. These findings suggest that early intervention with continuous terbutaline in the ED could decrease acute respiratory failure in severe exacerbations of pediatric asthma.

Treatment Considerations

As new treatments emerge, special considerations must be made to minimize adverse effects of therapy and to identify patients who could be particularly vulnerable to these untoward effects. Currently, there are limited data on whether patients with asthma are at high risk for bone loss, independent of oral corticosteroid use. Jung et al¹⁹ conducted a retrospective cross-sectional study of 7,034 patients who had undergone an extensive health checkup program in Seoul National University Hospital and had no history of oral steroid use. They found that patients with airway hyperresponsiveness (AHR; 3.1% of the study population) had significantly lower bone mineral density in the lumbar spine and femur compared with those without AHR. After adjusting for variables, such as smoking status and hormone replacement therapy, the proportion of patients with osteopenia and osteoporosis was

larger in the AHR-positive group (OR 1.7) compared with the non-AHR group. The risk also was higher in the ever-asthma group (OR 1.5) compared with the never-asthma group. Unfortunately, neither vitamin D levels nor ICS use were measured in the study. The investigators also found a propensity for bone loss in the presence of AHR, even after excluding patients diagnosed with asthma (and presumably those patients with a history of ICS use). They speculated that long-term vitamin D deficiency, and not ICS use, is likely a contributing factor to increased susceptibility for accelerated bone loss.

Conclusion

During the past year, we learned a great deal regarding the diagnosis and treatment of asthma. Several themes continue to emerge each year. These include the search for better tools in the stratification of disease control and better interventions to treat chronic disease and acute exacerbations. The message that is strongly being conveyed is that the illness we call asthma is really best described as a syndrome. Asthma is composed of multiple illnesses, with different levels of lability, triggers, response to therapy, and long-term sequelae. In the end, more research is needed and we as specialists treating this illness will have much more to read in the upcoming years.

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