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Year in review: pediatric allergy and asthma, excluding food allergy

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Introduction

This article discusses the epidemiology and evidence of known or proposed mechanisms of environmental, chemical, infectious, and perinatal exposures as they pertain to the development of pediatric allergy and asthma. This article will conclude by reviewing novel diagnostic techniques and therapeutic interventions to help clinicians mitigate asthma morbidity.

The prevalence of asthma is rising, affecting approximately 26 million people in the United States and nearly 9.6% of children in the United States.¹ The annual direct cost of asthma in the United States is \$50 billion, with the cost of an emergency department visit nearly 5 times the cost of an office visit.² Asthma does not affect all pediatric populations equally, with disproportionate burdens on children from minority and impoverished backgrounds.³

Risk Factors

Perinatal Influences

The German Perinatal Asthma and Environment Long-Term Allergy Study consisted of a comprehensive assessment of pregnancy-related and early life factors and asthma outcomes from birth through 5 years of age.⁴ Repeated common colds during pregnancy were associated with an increased risk of wheezing outcomes, independent of medication intake or concomitant fever.⁴ A review analysis by Ciaccio and Girdhar⁵ highlighted 2 studies that showed compelling protective evidence of maternal ω -3 fatty acid supplementation and infant allergy. The data suggested that offspring of women who took long-chain ω -3 polyunsaturated fatty acids during pregnancy and while breastfeeding had significantly

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lower odds of developing eczema. The investigators postulated potential protective mechanisms, such as through an “anti-inflammatory intestinal microbiome,” contributing to sensitization development.⁵ This article contributes to the conflicting literature of the role of fatty acids and pediatric allergy.

Chemical and Environmental Exposures

New evidence explores the effects of high- and low-molecular-weight phthalates, pesticides such as dichlorophenols, and broad-spectrum antimicrobials such as triclosan exposure and their impact on the microbiome and asthma development and morbidity. In addition to immunomodulatory effects, dichlorophenols are airway irritants. Using the US National Health and Nutritional Examination Survey, urinary dichlorophenol levels in the upper tertile were associated with atopic wheezing, physician-diagnosed asthma, worse asthma morbidity, and elevated IgE levels.⁶ A study with similar methodology, which used cumulative National Health and Nutritional Examination Survey data to assess the impact of triclosan on asthma prevalence and control, found an approximately 70% increased risk of reporting an asthma exacerbation in the last year in those with higher urinary triclosan metabolites.⁷ Multiple studies have suggested that urinary biomarkers of phthalates, specifically higher-molecular-weight phthalates, which are used in plastics, are associated with allergies and asthma.⁸ A review article by North et al⁸ highlighted that oxidative stress markers and phthalate metabolites in urine have recently been linked to decrements in pulmonary function, with effect modifications by polymorphisms in oxidative stress-related genes. This review stressed that oxidative stress-mediated lung dysfunction might be an important mechanism of phthalate toxicity related to asthma.⁸ Those with an allergic disease and/or asthma could have higher levels of dichlorophenols, triclosan, and phthalates because of increased medication or personal care product use. As a scientific community, we are unable to assume causation versus reverse causation without further longitudinal and immunologic studies.

Infectious Agents

Several prior epidemiologic studies and experimental models have suggested infection with *Toxocara canis*—roundworms of dogs—contributes to the development of allergic diseases.⁹ A pivotal meta-analysis conducted by Li et al,⁹ including 10 studies with more than 1,500 participants, suggested that a positive relation exists between *T canis* infection and asthma.

Illi et al⁴ demonstrated a consistent inverse association between wheezing and atopic outcomes and endotoxin levels in a child’s mattress. The effects of the endotoxin from a child’s bed might be due to reverse causation, and thus endotoxin might not be protective against the development of atopic outcomes; rather, children with atopy might have lower levels of endotoxin released from the gut or skin compared with children without atopy.

Comorbid Conditions

A Perspective piece by Permaul et al¹⁰ highlighted the proposed pathogenesis that links obesity and asthma and suggested a discrete clinical asthma phenotype in obese children that

differentiates them from the larger pediatric asthmatic population. Previous literature has demonstrated an association between obesity and the incidence, prevalence, and morbidity of asthma. A well-known cohort, the International Study of Asthma and Allergies in Childhood phase II in Germany, has provided conflicting evidence to this concept. This study showed that increases in body mass index from childhood to adolescence were linked to increased incidence and persistence of rhinitis but were not associated with increases in atopic or respiratory diseases universally.¹¹ Previous literature has demonstrated an association between obesity and prevalence and morbidity of asthma. Potentially, there might be a threshold for obesity to have a causative effect in triggering atopic disease, such as the extreme spectrum of obesity. A morbidly obese subset was not examined in this cohort.¹¹

Novel Diagnostic Techniques

Several articles in the *Annals* during 2014 focused on the evolving role of fraction of exhaled nitric oxide (FeNO) and asthma diagnostics, guiding medication treatment decisions in asthma care.^{12–16} FeNO monitors eosinophilic-mediated small airway inflammation and has been proposed as a potential biomarker for monitoring the progression of asthma.¹⁷ A review study published by Ritz and Trueba¹² found substantial evidence that anxiety, negative affect, and acute stress have a positive association with FeNO in asthma, whereas chronic stress and depression are more conflicting and were found to have an inverse association with FeNO. Proposed pathophysiologic mechanisms have suggested that these conflicting associations are mediated through other pathways such as increased oxidative stress or arginase resulting in decreased measurable FeNO.¹²

Articles published in the *Annals* have helped contribute to the ongoing discourse on the utility of FeNO measurements in routine asthma care. A study conducted by Chipps et al¹⁶ looked at a subset of the population with FeNO greater than 100 ppb, and a study by LaForce et al¹⁴ examined the impact of FeNO on clinical decision making. Most importantly, these small observational studies highlighted the need for randomized controlled longitudinal studies to further understand the role of FeNO in the pediatric and adult populations. If studied further, FeNO has the potential to guide treatment decisions to result in decreased asthma morbidity and health care usage.^{14–16} Three articles focused on the utility of the noninvasive Asthma Predictive Index, the role of methacholine challenge tests, and thresholds of provocative concentrations, respectively, and the ability of each to diagnose and guide treatment decisions in patients with mild asthma.^{18–20}

Therapeutic Interventions

The role of omalizumab, anti-IgE therapy in severe refractory asthma and respiratory diseases in general, was highlighted in the 2014 issues of *Annals*. A review study by Bonini et al²¹ focused on the evidence behind omalizumab in the treatment of respiratory diseases. This review referenced a 28-week randomized double-blinded, placebo-controlled trial in patients with moderate to severe asthma, which demonstrated a significant decrease in asthma exacerbations and improvements in asthma and rhinitis symptom scores.²¹ Although a US Food and Drug Administration safety subcommittee and the United Kingdom National

Institute for Health and Clinical Excellence voted in favor of recommending omalizumab in children 6 to 11 years of age, this therapy is still awaiting formal approval in this age group.²²

Several studies also focused on the potential benefit of heliox-driven nebulized β_2 -agonists and early administration of intravenous β -agonists, such as terbutaline, on asthma outcomes.^{23–25} A pivotal promising review and meta-analysis conducted by Rodrigo and Castro-Rodriguez²⁵ indicated that among the 3 pediatric studies, β_2 -agonist heliox-driven nebulization significantly decreased the severity of exacerbations in children as measured by asthma or pulmonary severity composite scores. Pooled analysis of 7 trials, which included children, showed significantly lower rates of hospital admissions. This meta-analysis concluded that treatment of 9 patients with this heliox delivery method prevented 1 patient from undergoing hospitalization compared with standard oxygen-driven nebulization.²⁵ A retrospective study conducted by Doymaz et al²⁴ suggested that early administration of intravenous terbutaline in pediatric asthma significantly decreased respiratory failure and need for mechanical ventilation in the largest cohort to date of pediatric patients with severe asthma.^{23,24} One limitation of this study is that, in addition to early administration of intravenous terbutaline, the treatment vs control groups initiated their medical care at different medical facilities. However, this study corroborated previous work that suggests the response to inhaled bronchodilators varies with severity of airway obstruction and highlighted the need for larger prospective trials of intravenous β -agonists in the emergency management of severe pediatric asthma exacerbations.²⁴

Conclusion

This year in review highlights a portion of the articles related to pediatric allergy and asthma in the *Annals* in 2014. The next year has the promise of answering several pivotal questions related to exposure, at-risk populations, and the evolving diagnostic and therapeutic areas of asthma care.

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