

Advances in asthma 2015: Across the lifespan



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In 2015, progress in understanding asthma ranged from insights to asthma inception, exacerbations, and severity to advancements that will improve disease management throughout the lifespan. 2015's insights to asthma inception included how the intestinal microbiome affects asthma expression with the identification of specific gastrointestinal bacterial taxa in early infancy associated with less asthma risk, possibly by promoting regulatory immune development at a critical early age. The relevance of epigenetic mechanisms in regulating asthma-related gene expression was strengthened. Predicting and preventing exacerbations throughout life might help to reduce progressive lung function decrease and disease severity in adulthood. Although allergy has long been linked to asthma exacerbations, a mechanism through which IgE impairs rhinovirus immunity and underlies asthma exacerbations was demonstrated and improved by anti-IgE therapy (omalizumab). Other key molecular pathways underlying asthma exacerbations, such as cadherin-related family member 3 (CDHR3) and orosomucoid like 3 (ORMDL3), were elucidated. New anti-IL-5 therapeutics, mepolizumab and reslizumab, were US Food and Drug Administration approved for the treatment of patients with severe eosinophilic asthma. In a clinical trial the novel therapeutic inhaled GATA3 mRNA-specific DNzyme attenuated early- and late-phase allergic responses to inhaled allergen. These current findings are significant steps toward addressing unmet needs in asthma prevention, severity modification, disparities, and lifespan outcomes. (*J Allergy Clin Immunol* 2016;138:397-404.)

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Abbreviations used

ACOS:	Asthma–chronic obstructive pulmonary disease overlap syndrome
ACQ:	Asthma Control Questionnaire
CDHR3:	Cadherin-related family member 3
COPD:	Chronic obstructive pulmonary disease
DNzyme:	DNA enzyme
FDA:	US Food and Drug Administration
HRV:	Human rhinovirus
ICS:	Inhaled corticosteroid
OR:	Odds ratio
ORMDL3:	Orosomucoid like 3
RSV:	Respiratory syncytial virus

In previous years, we provided separate reviews of pediatric and adult asthma publications in the previous year.^{1,2} This year, we directed our attention to asthma across the lifespan by combining these 2 age groups. Early-life events and exposures, even *in utero*, can play a significant role in the natural history of asthma, emerging into persistent, problematic, and/or chronic obstructive pulmonary disease (COPD) in certain subjects. Identifying these at-risk subjects at the earliest possible time for early intervention could optimize lifespan outcomes. In asthmatic patients this relates to prevention of asthma exacerbations, lung function decrease, and even disease onset.

In 2015, the *Journal* included more than 200 publications related to asthma. Because we cannot give each of these important publications appropriate attention, we have focused this review on 4 key areas that inform and will reshape asthma research and management in the coming years, and included relevant publications from other journals that help put these contributions into perspective: (1) inception, (2) exacerbations, (3) severity, and (4) selected topics, including disparities and asthma during pregnancy.

INCEPTION Environmental determinants

Several recent articles have discussed potential environmental influences on asthma inception. In a longitudinal birth cohort associations between infant over-the-counter antipyretics (acetaminophen and ibuprofen) and increased risk of childhood asthma were lost or attenuated when adjusted for upper respiratory tract infections, which themselves were a stronger risk factor for childhood asthma, and demonstrated the importance of adjusting for upper respiratory tract infections in such studies.³ In another

birth cohort prenatal maternal urinary bisphenol A and high-molecular-weight phthalate metabolites increased the relative risk of self-reported wheeze, chest infections, and bronchitis.⁴

Microbiome

Knowledge regarding the establishment, constituents, critical time periods, and disruption of the external, intestinal, and respiratory microbiome in relationship to asthma and atopy inception continued to be a strong thematic area of research in 2015. The epidemiologic observations behind the hygiene hypothesis were linked to the evolving microbiome story in a review by Liu.⁵ A Current perspectives article by Huang and Boushey⁶ focused on airway microbiome differences in asthmatic patients, as well as the association of different microbiome environments and asthma development. The article reviewed the concept of the “common mucosal response,” which suggests stimulated immune responses at one mucosal site can influence alternative mucosal sites. The same group looked at features of the bronchial microbiome in patients with severe and mild-to-moderate asthma and healthy control subjects.⁷ Differences in airway bacterial composition in patients with severe asthma were found: Proteobacteria was associated with worsening Asthma Control Questionnaire (ACQ) scores and total sputum leukocyte values, an abundance of Bacteroidetes/Firmicutes was positively correlated with body mass index, and Actinobacteria was associated with improving/stable ACQ scores. Davis et al⁸ analyzed 2001-2004 National Health and Nutrition Examination Survey data for associations between *Staphylococcus aureus* nasal colonization and asthma outcomes and found *S aureus* colonization was associated with asthma prevalence, symptoms, and exacerbations in children and young adults but not in adults older than 30 years. Although most data detail bacteria at the mucosal interface, helminths, viruses, and fungi represent other possible microbiome constituents affecting asthma outcomes. Viral infections have frequently been discussed in the context of wheezing and/or asthma exacerbations. By surveying twice-weekly nasal samples for 10 weeks in a group of asthmatic children, Tovey et al⁹ demonstrated that rhinovirus detection was also associated with increased day-to-day asthma symptoms. This accounted for 6% to 10% of the population-attributable risk in symptoms and suggests that other factors are also important to day-to-day symptom variability.

Understanding how the microbiome in infancy affects early immune development was furthered by current research. A prospective cohort study of the nasal microbiota in healthy infants using biweekly sampling demonstrated the personalized and dynamic nature of the nasal microbiota and put forth age and seasonality as key factors contributing to microbial composition.¹⁰ A review by Holt¹¹ on mechanisms of allergic disease focused specifically on the infant respiratory microbiome and atopic asthma development, covering background immunology with a useful historical perspective. The development of allergen sensitization, as well as the intersection between respiratory tract infections and the nasopharyngeal microbiome, on the development of persistent wheeze were included in this review.

The concept of critical windows for immune development and gut microbiome establishment during infancy were reinforced in an analysis of the gut microbiota of infants enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) longitudinal birth cohort study.¹² Three hundred nineteen children were selected for gut microbiome analysis at

3 and 12 months of age. Comparisons of relative taxa abundance according to 4 clinical phenotypes (patients with atopy plus wheeze, patients with atopy only, patients with wheeze only, and control subjects) were performed. The group with the highest risk for asthma (atopy plus wheeze) displayed lower abundances of the genera *Faecalibacterium*, *Lachnospira*, *Rothia*, and *Veillonella* exclusively at 3 months. To test the potentially protective microbial taxa, germ-free mice in an asthma model were inoculated with infant stool collected at 3 months of age from a patient with “atopy plus wheeze” or with the same stool supplemented with the 4 bacterial genera listed above. The progeny of the supplemented mice showed reduced airway inflammation.¹² Another intriguing observation in this study was the reduced level of fecal acetate in 3-month stool samples from participants with “atopy plus wheeze.” Acetate and other short-chain fatty acids are nutrients capable of protecting against airway inflammation through stimulation of regulatory T cells and dendritic cells, which can prevent T_H2-type immune responses.¹³ A protective gut microbiome might promote regulatory immune development and prevent airway inflammation by altering nutrient metabolism. For further reading regarding techniques of microbiome assessment, the establishment and modulation of the infant gut microbiome, as well as future directions in microbiome research, the reader is directed to the recent review by West et al.¹⁴

Sensitization patterns to allergen components

Although select allergens have surfaced as seemingly more important drivers of asthma morbidity than others, narrowing attention to only those exposures perceived to be most relevant overlooks the real-life experience of innumerable host-exposure interactions occurring simultaneously. Levels of serum IgE specific for 112 molecular components from 51 allergen sources were measured in 11-year-old participants of a population-based birth cohort to assess how complex multiallergen sensitization can influence atopic disease.¹⁵ Latent variable modeling revealed that allergen component sensitizations clustered into 3 groups (predominantly pollen, dust mite, and animal/food allergen groupings). Asthma was most strongly associated with sensitization to the animal/food allergen group; in particular, sensitization to lipocalins was associated with asthma. Although limited by its cross-sectional design, this study suggests specific sensitization patterns can influence or predict disease manifestations in patients with atopy.

Epigenetics

Methylation of CpG sequences in specific genes is one of the epigenetic mechanisms that alter gene expression. The epigenetic contribution to asthma expression can be appreciated in a genome-wide study of the methylation differences in PBMCs of black atopic asthmatic children compared with nonatopic nonasthmatic control subjects.¹⁶ Atopic asthmatic children had 81 differentially methylated gene loci, including hypomethylation of T-lymphocyte genes (eg, *IL13*, *RUNX3*, and *TIGIT*), and their related overexpression. Genetic variation in the orosomucoid like 3 (*ORMDL3*) gene is linked with rhinovirus-induced exacerbations, as discussed below.^{17,18} Differential methylation of CpG sites in *ORMDL3* was also associated with asthma and affected *ORMDL3* expression.¹⁹ In this study both *ORMDL3*

gene polymorphisms and differential methylation were independently associated with *ORMDL3* expression, explaining how genetic and epigenetic mechanisms can work in concert to affect asthma susceptibility gene expression. Histone acetylation is another mechanism of epigenetic transcriptional regulation. Atopic asthmatic children had higher IL-13 acetylation of peripheral blood CD4⁺ cells and related PBMC-stimulated IL-13 secretion.²⁰

EXACERBATIONS

Attaining control of asthma by minimizing future risk of exacerbations remains paramount in the treatment of asthma. Because exacerbations account for a substantial portion of the morbidity and mortality attributed to asthma and have been implicated in asthma persistence and progressive decrease in lung function, accurately predicting exacerbations is imperative to tailor preventive interventions and optimize outcomes across the lifespan.

Predicting exacerbations

Over the past year, key investigations have shed light on not only risk for an asthma exacerbation but also the risk for more severe exacerbations (Table I). To develop a predictive risk score for exacerbation, Bateman et al²¹ retrospectively studied nearly 7500 predominantly adult participants whose asthma symptoms were not controlled from 3 clinical trials while receiving Global Initiative for Asthma steps 3 and 4 controller treatment.²¹ In their multivariate analysis the level of controller therapy, reliever use, postbronchodilator FEV₁, body mass index, and 5-item ACQ score were significant predictors of asthma exacerbations within the subsequent 6 months, with an exacerbation risk of approximately 5% to 40%. Another study, this time within a closed health care network, also found a strong association between suboptimal asthma control and subsequent frequent exacerbations.²² To prospectively assess how asthma control can influence the severity of virus-induced exacerbations, Jackson et al²³ inoculated 28 adults of differing degrees of asthma control with rhinovirus. Irrespective of asthma severity or treatment status, more severe exacerbations were observed in those with uncontrolled asthma.

Because of significant seasonal variation in asthma exacerbations, predictors of impending exacerbation in a subsequent season were identified in an analysis of 400 children and young adults participating in studies chartered by the National Institute of Allergy and Infectious Diseases-sponsored Inner City Asthma Consortium.²⁴ Allergen sensitization and lung function were important predictors for all seasons, whereas the strongest predictor for the fall and winter seasons was a history of an exacerbation in the previous season, and the strongest predictor for the spring and summer seasons was a higher inhaled corticosteroid (ICS) requirement. The most robust model was developed for exacerbations that occurred in the fall season, when allergen sensitization and fraction of exhaled nitric oxide were more strongly associated with exacerbations than at other times of the year. This supports the hypothesis that the interaction of allergy, viral respiratory tract infections, and asthma exacerbations is especially strong in the fall season.

Preventing exacerbations

Efforts to predict asthma exacerbations dovetail with prevention studies. Prompted by the observation of seasonal

variations in asthma exacerbation frequency, the Preventive Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study compared the effects of initiating omalizumab, ICS boost, or placebo before the fall season in inner-city children and adolescents with asthma.²⁵ The addition of targeted 4-month treatment with omalizumab to guideline-based therapy resulted in a significant reduction in asthma exacerbations. Subgroup analysis revealed that this benefit was predominantly observed in patients with an exacerbation during the run-in phase and those with the highest-level controller therapy (Table I). For those without a preceding exacerbation, the clinical effect of adding omalizumab or an ICS boost was comparable with placebo.

Another compelling finding of this study was the effect of omalizumab on IFN- α responses to rhinovirus, a common and problematic trigger of asthma exacerbations. Within the omalizumab-treated group, IFN- α responses to rhinovirus were significantly increased. In addition, omalizumab-treated participants with increases in *ex vivo* IFN- α responses to rhinovirus had a significantly lower rate of exacerbation. An interesting limitation of the PROSE study is that 36% of children recruited based on severe asthma exacerbation in the prior year were ineligible because they were not allergen sensitized, suggesting a significant proportion of children experience severe exacerbations unrelated to allergen-specific IgE.

Although there are immediate benefits of preventing asthma exacerbations, including reducing health care resource use, long-term deleterious effects require further investigation. In the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study asthma exacerbations were associated with an annual decrease in lung function,²⁶ a decrease that appeared most prominent in children, suggesting a greater negative effect caused by asthma exacerbations in younger populations who have not yet achieved their peak FEV₁.

Other mechanisms of virus-induced exacerbations: *CDHR3* and *ORMDL3*

Multiple asthma susceptibility genes have been identified, including cadherin-related family member 3 (*CDHR3*), a cadherin-related gene expressed in airway epithelium linked to recurrent severe exacerbations in young children,²⁷ and *ORMDL3*, a sphingolipid biosynthesis regulator linked to human rhinovirus (HRV)-associated (and not respiratory syncytial virus [RSV]) wheezing illnesses in children.¹⁷ Research published in 2015 further elucidated how these gene polymorphisms affect asthma development. In patients with virus-induced exacerbations, HRV-C has been more prevalent than other respiratory tract viruses or rhinovirus groups.²⁸ In 2015, Bochkov et al²⁹ linked *CDHR3* as a binding site for HRV-C, allowing for HRV-C uptake and replication. Furthermore, the *CDHR3* gene variant associated with increased hospitalization risk for severe exacerbations conferred increased airway epithelial expression and 10-fold increases in HRV-C binding and replication (Table I). For *ORMDL3*, in addition to the previously identified polymorphism conferring HRV-associated exacerbation risk,¹⁷ Schedel et al¹⁸ identified 2 additional promoter region polymorphisms that were associated with asthma in children and conferred differences in transcription factor binding and transcriptional regulation of *ORMDL3* and T lymphocyte-stimulated secretion of the T_H2 cytokines IL-4 and IL-13.

TABLE I. Key advances in asthma in 2015

- Predictors of asthma exacerbations include allergen sensitization, exacerbations in the prior season, high-level controller requirement, and poor asthma control.
- Seasonal administration of anti-IgE (omalizumab) reduces fall seasonal exacerbations in school-aged children. The therapeutic effect was greatest in those with prior seasonal exacerbations and/or high controller treatment requirements and was related to improvement in impaired anti-viral IFN- α responses to rhinovirus.
- CDHR3 is an epithelial cell binding site for HRV-C, and the *CDHR3* gene variant associated with increased asthma hospitalization risk conferred increased airway epithelial expression of CDHR3 and large increases in HRV-C binding and replication.
- Fungal sensitization and exposure are associated with greater asthma severity, exacerbations, and airway IL-33–associated mechanisms.
- Anti-IL-5 mepolizumab (Nucala; GlaxoSmithKline, Brentford, United Kingdom) and reslizumab (Cinqair; Teva Pharmaceuticals, Petah Tikva, Israel) were FDA approved for the treatment of patients with severe eosinophilic asthma.
- In a clinical trial the novel therapeutic inhaled *GATA3* mRNA-specific DNzyme attenuated early- and late-phase allergic responses to inhaled allergen.

Treating early-life, respiratory virus–induced wheeze

Infection with select respiratory tract viruses, such as RSV and rhinovirus, in early life have been linked to increased asthma risk. For young children with significant respiratory symptoms from said viruses, optimal treatment and the long-term effects of treatment remain in question. In a randomized controlled trial 40 otherwise healthy infants hospitalized with RSV-induced bronchiolitis were treated with azithromycin or placebo for 14 days and subsequently followed for 12 months.³⁰ Azithromycin treatment during RSV-induced bronchiolitis reduced upper airway IL-8 levels, prolonged time to the third wheezing episode, and reduced overall respiratory morbidity over the subsequent year. Despite previous randomized controlled trials displaying negligible effects from macrolide use in this scenario, the long-term effects appreciated in this population were compelling.³¹ In terms of clinical outcome objective, a comparable study assessed the effects of prednisolone treatment (3 days) for a first, acute, moderate-to-severe, rhinovirus-induced wheezing episode in young children.³² Overall, no significant difference in long-term outcomes was appreciated. However, children with a rhinovirus load of greater than 7000 copies/mL had significantly less recurrence in the prednisolone compared with the placebo group.

SEVERITY

Severe asthma prevalence

In severe asthma characterization and management, it can be helpful to distinguish patients with severe asthma whose symptoms are poorly controlled despite being prescribed high-level controller treatment (eg, high-dose ICSs with long-acting bronchodilators) from those who are refractory to these conventional controller therapies. In a large Dutch pharmacy database survey investigators sought to estimate the prevalence of severe refractory asthma in asthmatic adults, who were defined as those with poor asthma control, severe exacerbations, or both while prescribed high-level controller therapy and having at least 80% adherence with prescription refills and additionally demonstrating good inhaler technique.³³ Although 17.4% of asthmatic adults had “difficult-to-control” asthma, meaning poor asthma control, severe exacerbations, or both while receiving high-level controller treatment, the prevalence of severe refractory asthma was 3.6% (ie, nearly 5-fold lower).

Severe asthma mechanisms

Within asthma lies a complex interplay between host and environment, with exposures significantly augmenting disease morbidity. Given the strong associations between dampness and mold in the home and respiratory health,^{34–36} as well as the unique immune responses elicited by fungal elements,³⁷ fungal sensitization remains a feature of interest in the characterization of asthmatic patients. In a meta-analysis and systematic review of relevant asthma studies, Sharpe et al³⁸ found pertinent fungal species, such as *Cladosporium*, *Alternaria*, *Aspergillus*, and *Penicillium*, were present at higher concentrations in homes of asthmatic participants, which corresponded with increased asthma symptoms. Examining this relationship further than association alone, Castanhinha et al³⁹ noted children with severe asthma with fungal sensitization had earlier symptom onset, higher total IgE levels, more maintenance oral steroid prescriptions, and increased airway IL-33 levels when compared with children with severe asthma without fungal sensitization. In their murine model *Alternaria alternata* exposure resulted in increased IL-33–mediated type 2 innate lymphoid cells, T_H2 cell numbers, and airway hyperresponsiveness that persisted despite budesonide therapy, recalcitrant features that were not appreciated with house dust mite exposure (Table I). In another study the T_H2-high phenotype of severe asthma was related to a single nucleotide polymorphism in *IL1RL1* that encodes and alters airway expression of the IL-33 receptor.⁴⁰ In another study the airway epithelial cells of patients with severe eosinophilic asthma, when stimulated with IL-13, produced high levels of the chemokine CCL26 (ie, eotaxin-3), and sputum CCL26 levels were strongly correlated with sputum eosinophil counts ($P < .0001$).⁴¹

Myofibroblasts are believed to have a role in airway remodeling in patients with severe asthma. Lo et al⁴² examined the survival, myofibroblastic differentiation, and CCR7 expression in blood fibrocytes of patients with severe and nonsevere asthma to study the effects of corticosteroids on fibrocyte function. They concluded that patients with severe asthma have increased numbers of circulating fibrocytes that show enhanced myofibroblastic differentiation and that are less responsive to the effects of corticosteroids. The same research group also reported that the CXCR4/CXCL12 chemokine receptor–chemoattractant axis contributes to fibrocyte chemotaxis in patients with asthma exacerbations, whereas the CCR7/CCL19 receptor–chemokine axis plays an important role in patients with chronic obstructive asthma, possibly through airway remodeling.⁴³

In children transcriptome profiling of peripheral blood leukocytes revealed distinct differences in the gene expression profiles of children with therapy-refractory versus controlled asthma.⁴⁴ In another study differences in gene expression and cell function were also observed in phenotypic allergic and nonallergic asthmatic children. Allergic asthmatic patients had increased PBMC regulatory T-lymphocyte numbers and function, with lower expression of innate immune regulatory genes.⁴⁵ In contrast, patients without allergic asthma had increased IL-1 β expression and IL-17–shifted proinflammatory immunity with increased neutrophil counts. In children with moderate-to-severe asthma, those with increased serum TNF- α levels and peripheral blood TNF- α expression had greater asthma severity, suggesting that some might benefit from anti-TNF- α –directed therapy.⁴⁶

Asthma–chronic obstructive pulmonary disease overlap syndrome

Authorities in asthma, COPD, and their potential overlap (eg, Helen Reddel, Chair, Global Initiative for Asthma Science Committee,⁴⁷ and Postma and colleagues⁴⁸) called for fuller characterization in research and practice to develop a precise definition for asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS) and identify opportunities for targeted treatment that can be summarized in guidelines for management. Ghebre et al,⁴⁹ using cluster analyses for sputum cellular and mediator profiles for asthma and COPD, distinguished 3 clusters: asthma predominant (eosinophilic with high T_H2 cytokine levels), COPD predominant (mixed eosinophils and neutrophils), and ACOS (neutrophils). This suggests that sputum cellular and cytokine profiling might help characterize and distinguish patients with ACOS. An accompanying editorial by Gelb and Nadel⁵⁰ encouraged further studies to confirm these observations and identify pharmacotherapy targets. Considering the potential for overlap of asthma and COPD, the therapeutic approach was reviewed by Barnes,⁵¹ who indicated that corticosteroid resistance is a feature of ACOS and that understanding the molecular mechanisms of this resistance can play a role in identifying novel therapeutic targets that can restore corticosteroid responsiveness.

Therapeutic advances for severe asthma

The effect of biologics on the management of asthma continues to make its way to clinical practice in 2015. Bioactive molecules contributing to the pathophysiology of asthma severity, including IgE, eosinophils, IL-4, and IL-13, have provided therapeutic targets that are leading to personalized treatment for severe asthma guided by biomarkers and patient phenotypes.⁵² Reviews explored the role of biologics targeting these molecules, including omalizumab, mepolizumab, reslizumab, lebrikizumab, and dupilumab, in the management of severe asthma in adult and pediatric patients.^{52–54} Targeting IgE, omalizumab demonstrated a reduction in asthma exacerbations in pediatric patients prone to exacerbations and receiving the highest level of controller therapy.²⁵

The US Food and Drug Administration (FDA) recently approved 2 eosinophil-targeted biologics, anti-IL-5 antagonists (IL-5–binding antibodies) for the treatment of severe eosinophilic asthma, as defined by peripheral blood eosinophil counts (Table I). In 2015, mepolizumab was approved for the treatment of patients 12 years

of age and older (FDA posted November 5, 2015: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lb1.pdf). Mepolizumab has been shown to reduce the rates of asthma exacerbations, improve FEV₁, and reduce maintenance oral steroid doses in this population.^{55,56} In 2016, reslizumab was FDA approved for the treatment of patients 18 years of age and older (FDA posted March 29, 2016: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033b1.pdf). Reslizumab was found to reduce asthma exacerbations, prolong the time to first exacerbation, and improve FEV₁ in patients with eosinophilic asthma.⁵⁷

A novel therapy for the treatment of T_H2-driven asthma targeted GATA3, a transcription factor that plays a key role in T_H2 cell differentiation, through an inhaled DNA enzyme (DNAzyme) that specifically cleaves and inactivates GATA3 mRNA.^{58,59} In a study of allergic asthmatic patients with sputum eosinophilia and biphasic early and late asthmatic responses after allergen provocation, inhalation of GATA3-specific DNAzyme once daily for 28 days attenuated both early and late asthmatic responses to allergen provocation when compared with placebo (Table I).⁵⁹ The GATA3-specific DNAzyme was safe and well tolerated in phase I clinical trials.^{58,59}

Although the previous therapies outlined have focused on atopic asthma, potential therapeutics for nonatopic asthma have also been investigated. The recombinant IL-1 receptor antagonist anakinra could be a future potential therapeutic candidate for the treatment of neutrophil-predominant asthma.⁶⁰ In a phase I study of healthy volunteers, anakinra was found to diminish airway neutrophilia and IL-1 β , IL-6, and IL-8 levels in response to endotoxin challenge compared with placebo.⁶⁰ Biologics can be particularly useful in adults because patients older than 30 years have higher rates of treatment failure with standard ICS controllers, with the failure rate increasing proportionally with age.⁶¹ However, it is also important to note that participants older than 30 years had significantly higher body mass index, lower fraction of exhaled nitric oxide, and lower lung function, suggesting severe disease processes in this age group.

Before biologics can be used in children, additional studies are required because limitations exist to extrapolating their pediatric use from adult studies.⁵³ Currently, the use of biologics in patients is considered only after failure of conventional controller therapies has been determined, with electronic adherence-monitoring devices to assess controller adherence being a promising new tool.⁵³

SELECTED TOPICS

Disparities

In addition to the deepening understanding of asthma pathogenesis, further insight into disparities in asthma outcomes among different populations has the potential to identify key areas for high-yield public health initiatives. Using a multivariate logistic regression model controlling for not only socioeconomic factors but also variable areas of residence (eg, urban, suburban, and metro), Keet et al⁶² demonstrated that asthma prevalence and morbidity were related to black race, Puerto Rican ethnicity, and lower household income but not residence in poor or urban areas. Asthma prevalence in inner-city versus non-inner-city areas was not significantly different after adjusting for race/ethnicity, region, age, and sex. Further evidence against inner-city locations *per se* as a risk factor for asthma prevalence was shown by Ownby

et al.⁶³ Their study compared African American youth in rural Georgia and urban Detroit with similar poverty and subsidized lunch rates. There were no significant differences in the prevalence of current diagnosed asthma or the prevalence of undiagnosed asthma between these groups. Although limited by self-reported data, these studies question the importance of residence in urban or inner-city locales and highlight the effect of race/ethnicity and income on asthma prevalence and morbidity.

Several patient characteristics were found to negatively affect asthma outcomes. Garcia et al⁶⁴ used an optimization model to calculate geographic access to pediatric primary and specialist care in Georgia and North Carolina. Their model demonstrated associations between access to care and emergency department visits for pediatric asthma. Patel et al⁶⁵ showed that asthmatic children had a greater prevalence of comorbidities compared with nonasthmatic children. Asthmatic patients with multiple chronic conditions had increased likelihood of asthma symptoms and all-cause emergency department visits.⁶⁵

Allergen immunotherapy

The effect of an established treatment, allergy immunotherapy, for asthma was addressed through an international consensus guideline based on scientific evidence and expert opinion.⁶⁶ The beneficial use of subcutaneous or sublingual immunotherapy for asthma, including reduction in medication use and symptoms, must be weighed against the side-effect risks. Newer forms of immunotherapy are in development using recombinant allergens in a continuing effort to reduce allergenicity while preserving immunogenicity and improving efficiency.⁶⁷

Asthma during pregnancy

Health care use during pregnancy and the effect of asthma medications on neonatal outcomes were examined. Based on health insurance claims, pregnant asthmatic patients had more asthma-related hospitalizations, which increased each trimester, but fewer outpatient visits than nonpregnant asthmatic patients.⁶⁸ Asthma exacerbations during pregnancy occurred in those who had increased asthma-related health care use in the prior year, but exacerbations had no associated adverse perinatal outcomes other than an increased rate of cesarean section.⁶⁸

An analysis of 13 European congenital anomaly registries, including 76,249 registrations, found that exposure in the first trimester to inhaled β_2 -agonists had a significantly increased odds of an association with cleft palate (odds ratio [OR], 1.63; 95% CI, 1.05-2.52) and gastroschisis (OR, 1.89; 95% CI, 1.12-3.20), and exposure to ICS-long-acting β -agonist combination therapy had an increased odds of renal dysplasia (OR, 3.95; 95% CI, 1.99-7.85).⁶⁹ The authors noted that the excess risk for these conditions in an individual woman is low and the use of ICSs in the first trimester appeared to be safe and concluded that “use of prophylactic inhaled steroids seems to be the best solution for treatment of asthma in pregnancy to prevent asthma exacerbations and to reduce the need for β_2 -agonists.”⁶⁹ In a cohort of moderate-to-severe pregnant asthmatic patients, the use of lower-dose ICS/long-acting β -agonist compared with a higher-dose ICS monotherapy treatment step counterpart in the first trimester showed a similar risk of major congenital malformation in both groups, suggesting both therapeutic options could be considered during pregnancy.⁷⁰ These studies

addressing medication use were based on prescriptions, limiting interpretation because they did not account for adherence.⁶⁸⁻⁷⁰ Analysis of the Xolair Pregnancy Registry showed that in 191 women with exposure to omalizumab either 8 weeks before conception or during pregnancy had no increased risk of major congenital anomalies, premature deliveries, or small-for-gestational-age or low-birth-weight infants compared with other asthmatic populations.⁷¹

CONCLUSIONS

In 2015, investigators refined understanding of the interplay between the environment, biologic responses, immune development, and genetic susceptibility, leading to the development of asthma exacerbations and severe phenotypes. Promising examples include how gut microbes provide nutrients (eg, short-chain fatty acids like acetate) for the development of immune regulation and protection against asthma in early life; the evidence that *CDHR3*, a gene linked to asthma exacerbations, is an epithelial receptor for HRV-C; and how IgE-crosslinking reduces innate immune responses to rhinovirus that is improved with anti-IgE therapy (Table 1). Such findings might seem far from improving the lives of asthmatic patients in need of better options today. 2015 is also notable for the FDA approval of 2 new anti-IL-5 therapeutics for severe eosinophilic asthma that exemplify how molecular discoveries can be fully realized as therapeutic options for providers and patients. Gains in understanding and reducing the severity and frequency of asthma exacerbations will help to reduce the risk and fear of asthma while potentially improving lifespan outcomes, especially considering recent evidence that exacerbations today reduce tomorrow's lung function. Although unmet needs in asthma prevention and disease modification remain, 2015's discoveries are substantiating asthma prevention clinical research and trials.

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