Year-in-Review

Year-in-review: Childhood asthma

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This review will highlight 2017 Journal publications. In 2017, numerous articles on the topics of pediatric asthma have been published. Because I cannot give each of the important publications appropriate attention, I have focused this review on 8 issues. Important issues over the past year included (1) Traffic-related air pollution increased the probability.[1] (2) Prenatal intake of vitamin D may protect against the development of recurrent childhood wheeze.[2] (3) The largest prospective cohort study in the United States and reported a 27% incidence of asthma development by age 5 years in children with severe bronchiolitis requiring hospitalization in their first year of life.[3] (4) Small-airways dysfunction can be detected as air-trapping with routine spirometric measures and can identify greater risk for asthma severity and instability in children.[4] (5) Inflammatory cells and different triggers are associated with 2 phenotypes of severe obstructive diseases during childhood: neutrophils and bacterial infection in preschool children and eosinophils and multiple allergies at school age.[5] (6) Blood eosinophils, bronchodilator responsiveness, body mass index, chronic sinusitis, and gastroesophageal reflux disease were found to be associated with exacerbation-prone asthma, after adjustment for age, sex, race, center, and medication adherence.[6] (7) In children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth.[7] (8) In children with allergic asthma, treatment with omalizumab decreased the duration of rhinovirus (RV) infections, viral shedding, and the risk of RV illnesses.[8]

Traffic-related air pollution and asthma trajectories

Childhood asthma is a heterogeneous and complex disease that is known to be exacerbated by environmental exposures, such as air pollution. To further understand the role of air pollution and

surrounding green spaces in childhood asthma etiology, it was examined that the annual occurrence and reoccurrence of asthma symptoms using contacts with medical practitioners for an asthma diagnosis to identify whether children followed different asthma trajectories, and to understand how air pollution and greenness may affect the likelihood of belonging to the identified trajectories.[1] Three distinct trajectories of asthma were identified using Group-based trajectory modeling of the annual prevalence of asthma in a population-based birth cohort study of 68,195 children followed from birth to age 10. Group-based trajectory modeling distinguished four trajectories: one with no asthma representing 88.8% of the cohort, one with transient asthma (5.6% of the cohort), and two trajectories with chronic asthma with early (1 yr; 1.5%) and late (3 yr; 4.1%) onset during early childhood. These trajectories differed with respect to socioeconomic markers and modifiable risk factors, including maternal smoking and breastfeeding initiation. After accounting for sex, parity, breastfeeding, term birth weight, household income, maternal education, delivery mode, and smoking, an interquartile increase in nitrogen dioxide exposure increased the risk of membership in the early and late-onset chronic asthma trajectories, relative to subjects without asthma, by 50% and 20%, respectively. Greenness was not associated with any of the asthma trajectories.

Prenatal Intake of Vitamin D and recurrent wheezing in children

Few observational studies suggest that vitamin deficiency is associated with developing higher prevalence of allergic diseases in children. 5 randomized controlled trials (RCTs) with a total of 2456 children were identified.[2] The systematic review of RCTs indicates that prenatal intake of vitamin D may protect against the development of recurrent childhood wheeze. There is lack of evidence on the effect of other vitamins for the prevention of respiratory and/or allergic outcomes.

Severe Bronchiolitis during Infancy and Risk of Asthma

A 20% to 60% risk of asthma in early childhood has been reported to be associated with severe bronchiolitis in infancy. Balekian et al[3] conducted the largest prospective cohort study in the United States and reported a 27% incidence of asthma development by age 5 years in children with severe bronchiolitis requiring hospitalization in their first year of life. Controlled for 12 asthma risk factors, severe bronchiolitis was associated with a 2.6-fold increased risk for asthma at 3 to 5 years. Promising primary prevention efforts such as palivizumab for respiratory syncytial virus prophylaxis in those at high risk for severe bronchiolitis and secondary asthma prevention interventions with azithromycin and omalizumab are being studied.156

Obstruction phenotype

The Asthma Phenotypes in the Inner City (APIC) study of the National Institute of Allergy and Infectious Diseases-sponsored Inner City Asthma Consortium evaluated a large set of variables among urban children to identify asthma clusters, factors related to difficulty in achieving asthma control, and the pathways linked to asthma severity. Small-airways instability resulting in premature airway closure has been recognized as a risk for asthma severity and poor control. Although spirometry has limited sensitivity for detecting small-airways dysfunction, a focus on the air-trapping component of obstruction might identify a risk factor for asthma instability. Prebronchodilation and postbronchodilation spirometric data were obtained from 560 children in the Asthma Phenotypes in the Inner City study.[4] An air-trapping obstruction phenotype (A Trpg) was defined as a forced vital capacity (FVC) z score of less than 21.64 or an increase in FVC of 10% of predicted value or greater with bronchodilation. The airflow limitation phenotype (A Limit) had an FEV1/FVC z score of less than 21.64 but not A Trpg. The no airflow limitation or air-trapping criteria (None) phenotype had neither A Trpg nor A Limit. The 3 obstruction phenotypes were assessed as predictors of number of exacerbations, asthma severity. in a cohort of inner-city children with protocol-guided asthma treatment, those meeting spirometric criteria for air-trapping require higher levels of treatment, experience more exacerbations, and have more airway lability compared with those who have airflow limitation without air-trapping and those with normal spirometric results at the time of evaluation. Small-airways dysfunction can be detected as air-trapping with routine spirometric measures and can identify greater risk for asthma severity and instability in children.

Severe childhood obstructive diseases

A better understanding of the asthma phenotypes and endotypes can help direct more personalized approaches to treat uncontrolled asthma. A prospective cross-sectional observational study that used cluster analysis to identify phenotypes in preschool (N = 217) and school age (N = 133) children with severe asthma identified 3 phenotypic clusters.[5] Children underwent standardized clinical and blood workup, and bronchoalveolar lavage (BAL) evaluation. Cluster 1 (39.4%), termed neutrophilic steroid-refractory recurrent wheeze, included patients with uncontrolled asthma despite high-dose ICS, more pneumonia and gastrointestinal reflux disease history, and higher blood neutrophil count. Cluster 2 (29.7%), termed severe recurrent wheeze with sensitization to 1 aeroallergen, consisted of patients with controlled asthma on high-dose ICS. Cluster 3 (30.7%), termed eosinophilic steroid-refractory asthma, included patients with uncontrolled asthma despite high-dose ICS who had more atopic characteristics (allergic rhinitis, atopic dermatitis, food allergies), and higher eosinophil count in both blood and bronchial alveolar lavage. Inflammatory cells and different triggers are associated with 2 phenotypes of severe obstructive diseases

during childhood: neutrophils and bacterial infection in preschool children and eosinophils and multiple allergies at school age.

Severe Asthma and Frequent Exacerbations

Although exacerbation prone patients with chronic obstructive pulmonary disease have been identified, this phenotype has not been systematically studied in asthma. The Severe Asthma Research Program (SARP)-3 is a National Institutes of Health/NHLBI network involving seven U.S. partnerships and a data coordinating center that is conducting studies to advance understanding of severe asthma through the integration of mechanistic studies with detailed phenotypic characterization procedures.6 This study describes the clinical, lung function, inflammatory, and comorbid characteristics of exacerbation-prone asthma in a well-phenotyped, multicenter cohort of patients of diverse age, enriched for severe disease. Of 709 subjects in the SARP-3 cohort, 294 (41%) had no exacerbations and 173 (24%) were exacerbation prone in the prior year. Several factors normally associated with severity (asthma duration, age, sex, race, and socioeconomic status) did not associate with exacerbation frequency in SARP-3; bronchodilator responsiveness also discriminated exacerbation proneness from asthma severity. In the SARP-3 multivariable model, blood eosinophils, body mass index, and bronchodilator responsiveness were positively associated with exacerbation frequency Chronic sinusitis and gastroesophageal reflux were also associated with exacerbation frequency, even after adjustment for multiple factors. Exacerbation-prone asthma is a distinct phenotype with prominent extrapulmonary features that may be modifiable.

Effects of Omalizumab on Rhinovirus Infections, Illnesses and asthma exacerbation

Allergic inflammation has been linked to increased susceptibility to viral illnesses, but it is unclear whether this association is causal. The PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study was designed to include weekly sampling for virology during the fall season, thereby providing a unique opportunity to test whether blocking IgE with omalizumab would reduce the severity of RV illnesses.[8] In the PROSE study, authors examined children with allergic asthma (aged 6–17 yr; n = 478) from low-income census tracts in eight U.S. cities, and they analyzed virology for the groups randomized to treatment with guidelines-based asthma care (n = 89) or add-on omalizumab (n = 259). Weekly nasal mucus samples were analyzed for RVs, and respiratory symptoms and asthma exacerbations were recorded over a 90-day period during the fall seasons of 2012 or 2013. Exacerbations were significantly associated with detection of rhinovirus C (OR, 2.85) and rhinovirus A (OR, 2.92), as well as, to a lesser extent, rhinovirus B (OR, 1.98). Omalizumab decreased the duration of RV infection (11.2 d vs.

12.4 d) and reduced peak RV shedding. Finally, omalizumab decreased the frequency of RV illnesses. In children with allergic asthma, treatment with omalizumab decreased the duration of RV infections, viral shedding, and the risk of RV illnesses. These findings provide direct evidence that blocking IgE decreases susceptibility to RV infections and illness.

Quintupling Inhaled Glucocorticoids and Asthma Exacerbations

Asthma exacerbations occur frequently despite the regular use of asthma-controller therapies, such as inhaled glucocorticoids. Clinicians commonly increase the doses of inhaled glucocorticoids at early signs of loss of asthma control. However, data on the safety and efficacy of this strategy in children are limited. The Randomized, double-blind, parallel group trial was conducted at 17 trial sites in the United States until March 2017.[7] This trial included 254 children, 5 to 11 years of age, who had mild-to-moderate persistent asthma and had had at least one asthma exacerbation treated with systemic glucocorticoids in the previous year. Children were treated for 48 weeks with maintenance low-dose inhaled glucocorticoids and were randomly assigned to either continue the same dose (low-dose group) or use a quintupled dose for 7 days at the early signs of loss of asthma control ("yellow zone"). Treatment was provided in a double-blind fashion. The primary outcome was the rate of severe asthma exacerbations treated with systemic glucocorticoids. The rate of severe asthma exacerbations treated with systemic glucocorticoids did not differ significantly between groups. The time to the first exacerbation, the rate of treatment failure, symptom scores, and albuterol use during yellowzone episodes did not differ significantly between groups. The total glucocorticoid exposure was 16% higher in the high-dose group than in the low-dose group. The difference in linear growth between the high-dose group and the low-dose group was −0.23 cm per year. In children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth.

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