Year-in-Review

Childhood asthma

Department of Pediatrics, Hallym University

Heysung Baek

This review will highlight 2016 Journal publications. In 2016, 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 5 issues. Important issues over the past year included (1) inhaled corticosteroid (ICS) as preferred 1st line controller in persistent disease[1] (2) intermittent high dose ICS effective in intermittent asthma[2] (3) acetaminophen and ibuprofen similar in safety in young children with mild persistent asthma[3] (4) Mild-moderate childhood asthma has substantial impact on lung function in early adulthood[4] (5) Safety of ICS/ Long-acting beta-agonists (LABA) combination therapy in children reassuring.[5]

Preschool Children

Many young children have asymptomatic periods between viral respiratory illnesses, raising the question of whether daily therapy with ICSs is warranted in all children because ICS administration does not significantly alter the long-term disease course[6] and might contribute to dose-dependent and sustained reductions in linear growth in selected subpopulations.[7] The Individualized Therapy for Asthma in Toddlers (INFANT) trial characterized phenotypic heterogeneity in young children with asthma necessitating treatment with daily controller medications (ie, Step 2 therapy2) and examined the relationship of phenotypic features and biomarkers to asthma medication response profiles.[1] This study demonstrates differential responses to asthma medications in young children that can be predicted with clinical biomarkers. Although young children requiring Step 2 asthma treatment are phenotypically diverse, children with aeroallergen sensitization and increased blood eosinophil counts respond best to a daily ICS, as opposed to an LTRA or an as-needed ICS.[1]

Optimal strategies for preventing severe exacerbations in preschoolers with recurrent wheeze population are not well defined. Systemic review and meta-analysis was performed to synthesize the evidence of the

effects of daily ICS, intermittent ICS, and montelukast as strategies for preventing severe exacerbations in preschool children with recurrent wheeze.[2] Kaiser SV et al[2] found strong evidence to support daily ICS for preventing severe exacerbations in preschool children with recurrent wheeze, specifically in children with persistent asthma. For preschool children with intermittent asthma or viral-triggered wheeze, they found strong evidence to support intermittent ICS for preventing exacerbations. With either treatment strategy, they recommend frequent reassessment of wheezing symptoms and pattern, close monitoring of growth, and active titration to the lowest ICS dose that is effective.[2]

Studies have suggested an association between frequent acetaminophen use and asthma-related complications among children, leading some physicians to recommend that acetaminophen be avoided in children with asthma[8-10]; however, appropriately designed trials evaluating this association in children were lacking. In a multicenter, prospective, randomized, double-blind, parallel-group trial, 300 children (age range, 12 to 59 months) with mild persistent asthma were enrolled and assigned to receive either acetaminophen or ibuprofen when needed for the alleviation of fever or pain over the course of 48 weeks.[3] Sheehan WJ et al[3] did not find that asthma exacerbations or other markers of asthma-related complications occurred more frequently among children who were randomly assigned to receive acetaminophen than among those who were randomly assigned to receive ibuprofen.

Bacteria and viruses were equally associated with the risk of acute episodes of asthma-like symptoms in young children, suggesting antibiotics as a potential treatment for such episodes in the Copenhagen Prospective Studies on Asthma in Childhood 2000 ($COPSAC_{2000}$; a previous birth cohort of children born to mothers with asthma).[11] At present, guidelines do not recommend antibiotics for treatment of early asthma-like episodes, yet they are widely used.[12] Hans Bisgaard et al[13] did a randomised controlled trial (RCT) of azithromycin for treatment of episodes of troublesome lung symptoms in young children who were followed up prospectively in new unselected Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$) birth cohort.[14] Azithromycin reduced the duration of episodes of asthma-like symptoms in young children, suggesting that this drug could have a role in acute management of exacerbations.[13] Further research is needed to disentangle the inflammatory versus antimicrobial aspects of this relation. Azithromycin Against Placebo in Exacerbations of Asthma (AZALEA) study investigated the effectiveness of azithromycin treatment when added to standard care for adult patients with asthma exacerbations.[15] In contrast to $COPSAC_{2010}$[13], azithromycin treatment resulted in no statistically or clinically significant benefit in symptoms, lung function, or speed of recovery.[15]

Phenotypes

Children living in low-income urban regions have high morbidity and asthma severity. Little is known about the asthma phenotypes in at-risk children and whether there are phenotypes that are less likely to

respond to specific interventions, including standard guidelines-based therapy. To meet this need, the National Institutes of Health/National Institute of Allergy and Infectious Diseases sponsored Inner-City Asthma Consortium Asthma Phenotypes in the Inner City (APIC) study were designed and conducted.[16] There was significant asthma heterogeneity among children living in low-income areas of US inner cities. Most asthma in this population appeared to cluster by the degree of allergy, rhinitis, allergic inflammatory markers, and impaired pulmonary physiology, with these factors worsening in parallel and correlating with more severe disease.[16] These findings provide a solid basis for personalized care where emphasis on environmental allergen management, allergen desensitization, and anti-TH_2 therapy is more appropriate for an allergic phenotype as opposed to the somewhat less-common persistently symptomatic phenotype with little allergy and inflammation.[16]

Lung Function

The Childhood Asthma Management Program (CAMP) cohort was followed from enrollment, at the age of 5 to 12 years, into the third decade of life, with at least annual prebronchodilator and postbronchodilator spirometry and detailed concomitant assessments.[4] The long follow-up offers the opportunity to examine the trajectory of lung growth and the decline from maximum growth in a large cohort of persons who had persistent, mild-to-moderate asthma in childhood and to determine the demographic and clinical factors associated with abnormal patterns of lung growth and decline. Impaired lung function at enrollment and male sex were the most significant predictors of abnormal longitudinal patterns of lung-function growth and decline. A pattern of reduced growth is evident early in childhood and can be expected to persist into adulthood. A total of 52% of patients with mild-to-moderate, persistent asthma have early lung-function decline, and 51% of those have no plateau phase. Identification of an abnormal trajectory by means of early and ongoing serial FEV1 monitoring may help identify children and young adults who are at risk for abnormal lung-function growth that might lead to chronic airflow obstruction in adulthood.[4]

Exacerbation

The Inner-City Asthma Consortium revealed insightful information about the risk factors for and treatment of asthma exacerbations of the high-risk understudied inner-city poor and minority child with asthma.[17] Specific risk factors included (1) allergic status and pulmonary function during all seasons, (2) the months immediately following an exacerbation, (3) atopy, and (4) the combination of allergic sensitization and specific allergen exposure, particularly to cockroach and rodents. Beneficial interventions that reduced exacerbations included (a) eradicating household allergens, although difficult to accomplish, (b) encouraging preemptive controller medication use in the summer months to prevent fall exacerbations, (c) applying

National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3-directed therapy to potentiate increased asthma control, and (d) implementing the anti-IgE biologic omalizumab.[17]

Safety of ICS/LABA combination therapy

LABAs have been shown to increase the risk of asthma related death among adults[18,19] and the risk of asthma-related hospitalization among children.[20-22] It is unknown whether the concomitant use of inhaled glucocorticoids with LABAs mitigates those risks. International, randomized, double-blind, active-comparator, 26-week trial from November 2011 through November 2015 at 567 trial centers in 32 countries was conducted.[5] In this trial involving children with asthma, salmeterol given in combination with fluticasone propionate did not result in a higher risk of severe asthma events among children 4 to 11 years of age than fluticasone alone.[5]

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