Clinical reviews in allergy and immunology

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Predicting asthma outcomes

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Activity Objectives:

1. To review the Asthma Predictive Index (API) and its modifications.
2. To identify factors associated with childhood asthma remission or persistence.
3. To describe the relationship between lung function and persistence of childhood asthma.

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This review addresses predictors of remission or persistence of wheezing and asthma from early childhood through adulthood. Early childhood wheezing is common, but predicting who will remit or have persistent childhood asthma remains difficult. By adding parental history of asthma and selected infant biomarkers to the history of recurrent wheezing, the Asthma Predictive Index and its subsequent modifications provide better predictions of persistence than simply the observation of recurrent wheeze. Sensitization, especially to multiple allergens, increases the likelihood of development of classic childhood asthma. Remission is more likely in male subjects and those with milder disease (less frequent and less severe symptoms), less atopic sensitization, a lesser degree of airway hyperresponsiveness, and no concomitant allergic disease. Conversely, persistence is linked strongly to allergic sensitization, greater frequency and severity of symptoms, abnormal lung function, and a greater degree of airway hyperresponsiveness. A genetic risk score might predict persistence more accurately than family history. Remission of established adult asthma is substantially less common than remission during childhood and adolescence. Loss of lung function can begin early in life and tracks through childhood and adolescence. Despite therapy which controls symptoms and exacerbations, the outcomes of asthma appear largely resistant to pharmacologic therapy. (J Allergy Clin Immunol 2015;136:829-36.)

Key words: *Asthma, birth cohorts, longitudinal phenotypes, lung function, persistence, prediction, remission, wheezing*

Symptoms of asthma most commonly begin in childhood, often in the first few years of life. Between 30% and 50% of preschool children experience episodes of wheezing, of whom less than half will have continuing childhood asthma. Over the last several decades, longitudinal studies have provided substantial information regarding the development and trajectories of childhood wheezing and the likely outcomes of different phenotypes of asthma. This review addresses 2 principal questions: first, can we predict which children with early childhood wheeze (often called preschool wheeze) will go on to have childhood asthma, and second, can we predict which children or adults with established asthma will experience remissions or relapse or have persistent asthma?

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Abbreviations used
ALSPAC: Avon Longitudinal Study of Parents and Children
aOR: Adjusted odds ratio
API: Asthma Predictive Index
BAMSE: Barn/Children, Allergy and Milieu in Stockholm, an Epidemiological study
CAMP: Childhood Asthma Management Program
COPD: Chronic obstructive pulmonary disease
GRS: Genetic risk score
mAPI: Modified Asthma Predictive Index
OR: Odds ratio
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
PPV: Positive predictive value
ucAPI: University of Cincinnati Asthma Predictive Index

PREDICTING OUTCOMES OF EARLY CHILDHOOD WHEEZING

An Asthma Predictive Index (API) was proposed by Castro-Rodriguez[1] to provide a framework to predict outcomes of early childhood wheezing. Drawing on data from the Tucson Birth Cohort, the API uses 2 major criteria (physician-diagnosed parental asthma and physician-diagnosed childhood eczema) and 3 minor criteria (physician-diagnosed allergic rhinitis, wheezing apart from colds, and blood eosinophilia ≥4%) as predictors. The "stringent" index for prediction of asthma requires early frequent wheeze (≥3 episodes per year in 2- to 3-year-olds) and the presence of at least 1 of the 2 major criteria or 2 of 3 minor criteria. The "loose" index required less than 3 episodes per year, again combined with one of the major criteria or 2 of the minor criteria (Table I).

The usefulness of the API has been challenged on several grounds.[2] It predicts the outcome of asthma ever and not recurrent wheeze, which is more clinically relevant and of greater concern to physicians and families. The predictive value is highly dependent on the prior probability (prevalence) of asthma in the cohort in which it is used. The higher the prevalence of asthma (eg, in high-risk populations), the poorer will be the performance on the API in predicting the outcome of preschool wheeze. The usefulness of the API has also been challenged on the grounds that it has yet to be shown that identification of children with a positive API results in interventions or treatments that reduce later asthma, although this would be the desirable benefit of such identification.[3]

The Tucson-derived API has been validated in the Leicester birth cohort.[4] Using the loose API, the odds ratios (ORs) for asthma at age 7 were comparable (5.2 in Leicester and 5.5 in Tucson), and the positive predictive value (PPV) was 26% in both studies. For the stringent API, ORs were 8.2 and 9.8 and PPVs were 40% and 48%, respectively. These values were somewhat greater that those achieved by using a simple early wheeze criterion; in the Leicester cohort the OR for later asthma was 5.4 and the PPV was 21%, and for early frequent wheeze the values were 6.7 and 36%, respectively.

The API has undergone a number of modifications. The modified Asthma Predictive Index (mAPI) requires 4 or more wheezing episodes in the last year, adds another major criterion (sensitized to ≥1 aeroallergen), and changed the minor criteria by removing allergic rhinitis but adding sensitization to milk, egg, or peanut. The mAPI was evaluated in the Childhood Origins of Asthma cohort.[5] Prediction of school-age asthma improved from ages 1 to 3 years, and the mAPI provided a high likelihood ratio of 4.9 for asthma at 6 years and even higher for older children, with likelihood ratios of up to 55 at age 11 years. Decreasing the required number of wheezing episodes from 4 or more in the past year to only 2 episodes (the m^2API) decreased the predictive value and did not improve the predictive value of a negative test result.

In a high-risk prospective birth cohort, the Cincinnati Childhood Allergy and Air Pollution study, Amin et al[6] assessed another modified API, the University of Cincinnati Asthma Predictive Index (ucAPI). This was based on 2 or more episodes of wheeze in the last 12 months at age 3 years and 1 of 3 major criteria (parental asthma, allergic sensitization to ≥1 aeroallergen, and history of eczema) or 2 of 3 minor criteria (wheezing without a cold, allergic rhinitis, and milk or egg sensitization). The ucAPI was compared with a history of persistent wheezing at age 3 years (defined as ≥2 episodes of wheezing in the last 12 months at both the 2- and 3-year visits) as a predictor of objectively confirmed asthma (symptoms and a positive bronchodilator or methacholine response) at age 7 years. Confirmed asthma at 7 years was significantly associated with both a positive ucAPI (adjusted odds ratio [aOR], 13.3; 95% CI, 7.0-25.2) and the persistent wheezing phenotype (aOR, 9.8; 95% CI, 4.9-19.5).

A Task Force of the European Respiratory Society proposed the terms *episodic wheeze* to describe children who wheeze intermittently, apparently with viral infections, and who are well between episodes and *multitrigger wheeze* to describe children who wheeze both during and outside discrete episodes.[7] It was noted that there might be a large overlap in these phenotypes that could change over time. The debate on whether episodic wheeze and multitrigger wheeze differ in clinical features and whether differentiating these subtypes helps predict asthma at school age emphasized the limitations of predictive indices.[8] Triggers might be difficult to identify precisely. In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort, episodic wheeze and multitrigger wheeze did not correspond to specific longitudinally derived wheezing phenotypes identified by using longitudinal latent class analysis or hypothesis-based definitions of transient early and persistent wheeze.[8]

Recommendation for improving the API include more precise definitions of risk factors, such as sensitization (quantitative levels of IgE or multiple allergen sensitization); lung function; inclusion of maternal exposures, such as smoking and viral infections; more precise phenotyping of asthma with objective measurements; addition of noninvasive markers of inflammation; and better characterization of genetic risk and epigenetic effects.

Among high-risk children with a family history of atopic disease, the nature of the viral illness associated with early childhood wheezing had value in predicting the likelihood of persistence.[9] Contrary to previous understanding, wheezing illnesses associated with rhinovirus infection were more strongly associated with asthma at age 6 years than respiratory syncytial virus–associated wheezing illnesses. Almost 90% of children with rhinovirus-associated wheezing in year 3 had asthma at age 6 years.

Caudri et al[10] reported follow-up of 3963 children in the PIAMA cohort to age 8 years. Of these children, 55% had wheezing or coughing at night without a cold or both by age 4 years, but only 11% had asthma at age 7 to 8 years. Factors independently predicting asthma in later childhood included male sex, postterm delivery, medium or low parental education, parental use of inhaled medication, frequency of wheeze, wheezing/dyspnea