The Asthma Predictive Index: A very useful tool for predicting asthma in young children

Jose A. Castro-Rodriguez, MD, PhD *Santiago, Chile*

Recurrent wheezing is a common problem in young children: approximately 40% of children wheeze in their first year of life. However, only 30% of preschoolers with recurrent wheezing still have asthma at the age of 6 years. Nevertheless, asthma, the most prevalent chronic disease in children, is difficult to diagnose in infants and preschoolers. This article reviews the importance of determining at an early age which infants/preschoolers will have asthma later in life, analyzes the pros and cons of different predictive indices, and discusses the efficacy of the Asthma Predictive Index. (J Allergy Clin Immunol 2010;126:212-6.)

Key words: *Infants, preschoolers, wheezing, asthma, clinical score, asthma predictive index*

Which infants/preschoolers with recurrent wheezing will have asthma at school age? This is an important question; asthma, the most prevalent chronic disease in children, is one of the most difficult disorders for physicians to diagnose in infants/preschoolers. Approximately 40% of all young children worldwide have at least 1 episode of asthmatic symptoms, such as wheezing, coughing, or dyspnea.[1,2] Moreover, approximately 80% of the asthmatic subjects have the disease in the first years of life.[3] However, only 30% of preschoolers with recurrent wheezing still have asthma at the age of 6 years.[4] Recent data from the National Center for Health Statistics[5] showed that even though asthma prevalence was lower among preschool-aged children compared with school-aged children and adolescents, ambulatory care visits, emergency department visits, and hospital discharges were considerably greater for infants/preschoolers (0-4 years). A Swiss study[6] showed that children less than 3 years of age had significantly worse asthma control (more sleep disturbance, limitations in play and family activities, emergency department or general practitioner visits, and hospitalizations) compared with school-children and adolescents. This article reviews the importance of determining at early ages which infants/preschoolers will have asthma later in life and proposes the use of the Asthma Predictive Index (API) to identify these children.

From the Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Catolica de Chile.

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Reprint requests: Jose A. Castro-Rodriguez, MD, PhD, Lira 44, 1er. Piso, casilla 114-D, Santiago, Chile. E-mail: jacastro17@hotmail.com.

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Abbreviation/Acronyms used

API: Asthma Predictive Index
FeNO: Fraction of exhaled nitric oxide
mAPI: Modified Asthma Predictive Index
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
RCT: Randomized clinical trial

BACKGROUND

Unfortunately, infants who wheeze and eventually have asthma coexist with a large group of infants with recurrent wheezing whose symptoms are transient and usually subside during early years of school. It is a challenge to distinguish between these groups during infancy and early childhood simply on the basis of clinical presentation. No accurate screening tests (using genetic or single biochemical markers) have been developed to determine which young children with recurrent wheezing will have asthma.[7] Chronic inflammation is the most common feature of asthma, but measurements of inflammation are not yet a major factor in diagnosing and monitoring asthma. The best measurements of airway inflammation are made by using bronchoscopy with analysis of biopsy specimens, bronchoalveolar lavage samples, or both, procedures that are too invasive for routine use in children. Other noninvasive techniques (eg, measuring biomarkers of inflammation in exhaled breath condensate) are being tested in longitudinal studies for their efficacy in early diagnosis of asthma.[8] Therefore the diagnosis and management of asthma in young children are primarily based on subjective clinical features and findings from medical examinations.

A study of 95 children in Australia found that airway responsiveness at 1 month of age is a good predictor of airway function and lower respiratory tract symptoms at the age of 6 years.[9] However, a study of 129 children in France showed, after multivariate analysis, that early bronchial hyperresponsiveness in infants who wheezed did not predict the persistence of asthma between 5 and 9 years of age; in contrast, family history of atopy was the only significant risk factor.[10] Other studies showed that wheezing in the first 3 years of life was a poor predictor of subsequent asthma; instead, atopy in early life predicted future airway disease.[11,12] Matricardi et al[13] investigated the outcomes of wheezing using the Multicentre Allergy Study, a birth cohort study of 1,314 infants selected based on increased levels of IgE in cord blood, at least 2 atopic family members, or both.[13] They associated wheezing at the age of 13 years with atopy in parents and IgE sensitization to common allergens, increased total IgE levels, and exposure to high levels of indoor allergens in the first 3 years of life. A different study reported that serum levels of soluble IL-2 receptor (a sophisticated biomarker) predicted persistent wheezing for at least 12 months among atopic infants.[14] On the contrary, the

Major Criteria	Minor Criteria
1. Parental MD asthma †	1. MD allergic rhinitis §
2. MD eczema ‡	2. Wheezing apart from colds
	3. Eosinophilia (≥4%)

*Loose index for the prediction of asthma: early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the prediction of asthma: early frequent wheezer plus at least one of the two major criteria or two of three minor criteria.

†History of a physician diagnosis of asthma. ‡Physician diagnosis of atopic dermatitis at age 2 or 3. §Physician diagnosis of allergic rhinitis at age 2 or 3.

FIG 1. Asthma Predictive Index.*[15]

risk for transient wheezing during the first 3 years of life among children who did not wheeze by school age included low baseline levels of lung function, maternal smoking during pregnancy, and lower maternal age.[4]

API AND OTHER INDICES

The API was developed 10 years ago by using data from 1246 children in the Tucson Children's Respiratory Study birth cohort. It was based on factors that were found during the first 3 years of life to predict continued wheezing at school age.[15] A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physician-diagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia ≥4%). A loose index (<3 episodes/y and 1 of the major or 2 of the minor criteria) and a stringent index (≥3 episodes/y and 1 of the major or 2 of the minor criteria) were created (Fig 1).[15] A positive stringent API score by the age of 3 years was associated with a 77% chance of active asthma from ages 6 to 13 years; children with a negative API score at the age of 3 years had less than a 3% chance of having active asthma during their school years.

After the API was created, other scores were developed to predict which preschoolers with recurrent wheezing would have asthma at school age. In 2003, Kurukulaaratchy et al[16] used data from 1456 children in the Isle of Wight birth cohort to devise a scoring system based on 4 factors: family history of asthma, recurrent chest infections in the second year of life, atopic sensitization at 4 years of age, and absence of recurrent nasal symptoms in the first year of life. These factors confer a high risk for wheezing persistence at 10 years of age.

In 2008, Devulapalli et al[17] performed a nested case-control study of 449 children in Norway and created a simple scoring system based on obstructive airway disease scores: scores of 5 or greater (range, 1-12) by 2 years of age are a risk factor for asthma at 10 years of age. In 2009, Caudri et al[18] developed a clinical scoring system using data from 3963 children from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort in The Netherlands, in which participants were assessed on a yearly basis until the age of 8 years. Using data from a subgroup of children with reported wheezing or coughing at night (without a cold) until 4 years of age, they assessed possible predictors for asthma at 7 to 8 years of age. They found that male sex, postterm delivery, parental education, inhaled medication, wheezing frequency, wheezing/dyspnea apart from colds, respiratory tract infections, and eczema all independently predicted asthma. The authors established a risk score based on these 8 clinical parameters (cutoff of ≥20 as a positive value).

These 3 asthma indices are based on diverse variables,[15,16,18] and that condition could make a difference as to which index would have more success in different populations worldwide. The API has 5 parameters, whereas the Isle of Wight and PIAMA indices have 4 and 8 parameters, respectively (Table I).[15,16,18] Two studies included some reference to a family history of asthma.[15,16] Only 2 studies mention eczema,[15,18] nasal symptoms,[15,16] wheezing apart from colds,[15,18] or respiratory tract/chest infections.[16,18]

Children who experience early onset of allergic sensitization and respiratory tract illnesses that include wheezing are believed to be at the highest risk for persistent asthma. However, it is possible that recurrent chest infections identified in the Isle of Wight study or respiratory tract infections reported by the PIAMA cohort were actually misreported episodes of recurrent wheezing[19]; the definition of respiratory tract/chest infection might vary among populations. Because the relationship between virus-induced wheezing and asthma depends on the virus (eg, infants who wheeze from infection with rhinoviruses have a high risk for subsequent asthma) and because information about virus types was not reported for the Isle of Wight and PIAMA cohorts, further research is needed to identify viral factors that lead to asthma. In addition, the use of inhaled medication and level of parental education[18] depend on local public health strategies and social opportunities, respectively. Sex was included as a risk factor in 1 index.[18] The prevalence of asthma among each sex varies with age; in the first years of life, asthma is more prevalent in boys, but in adolescents it predominates among female subjects. Moreover, there are sex differences in the experience of asthma-like symptoms, the diagnosis of asthma, and the use of asthma medications.[20]

Several years ago, it was reported that allergic sensitization to aeroallergens and foods in early life was associated with asthma at school age.[21,22] More recently, a study from Germany found that asthma among subjects who were 7 to 22 years of age was associated with allergic sensitization by a specific IgE during the first 2 years of life but only if a positive parental history of asthma was present.[23] Among biomarkers used in the asthma predictors described above, eosinophilia is a minor criterion for asthma diagnosis in the API,[15] and allergic sensitization, based on skin prick test response, is a criterion of the Isle of Wight index.[16] A modified API (mAPI),[24] which was tested in a randomized trial of 285 subjects, incorporated allergic sensitization to 1 or more aeroallergens as a major criterion and allergic sensitization to milk, eggs, or peanuts as a minor criterion, replacing physician-diagnosed allergic rhinitis from the original API. However, the API, rather than the mAPI, is used to predict asthma in longitudinal studies.[25,26] In most health care settings, it is easier, cheaper, and probably more reliable (allergens vary with region) to determine eosinophilia counts in blood samples than to determine allergic sensitization with a skin prick test or by measuring specific IgEs. The members of the Multicentre Allergy Study performed multiple skin and IgE tests on subjects throughout childhood and used mathematic modeling to show that specific IgE responses did not reflect a single phenotype of atopy; only atopy to multiple factors at early ages predicted asthma at the age of 8 years.[27]

The ability of a segmentation mathematic model of analysis to predict asthma was tested in France with infants less than 30 months of age who had recurrent wheezing. It showed that a lack