The Asthma Predictive Index: early diagnosis of asthma

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Current Opinion in Allergy and Clinical Immunology 2011, 11:157–161

Purpose of review

Recurrent wheezing is a common problem in young children.

Recent findings

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.

Summary

We review the importance of determining at early age which infant/preschoolers will develop asthma later on life and discuss the utility of the Asthma Predictive Index.

Keywords

asthma, Asthma Predictive Index, infants, preschoolers, wheezing

Curr Opin Allergy Clin Immunol 11:157–161

1528-4050

Introduction

Although asthma is the most prevalent chronic disease in children and starts in the majority of the cases before the age of 5 years [1], it is still one of the most difficult disorders for physicians to diagnose in infant/preschoolers. This is due in part because in this age group, the clinical symptoms of asthma are variable and nonspecific because other wheezing disorders coexist [2,3], and neither airflow limitation nor airway inflammation, the main pathologic hallmarks of the condition, can be assessed routinely in this age group.

We know that approximately 40% of all young children worldwide have at least one episode of asthmatic symptoms such as wheezing, coughing, or dyspnea [2,3]; but only 30% of preschoolers with recurrent wheezing still have asthma at the age of 6 years [4]. However, asthmatic preschoolers had more morbidity (higher ambulatory care visits, emergency department visits, and hospital discharge) [5] and worse control (more sleep disturbance, limitations in play and family activities, emergency department or general practitioner visits, and hospitalizations) [6] compared with asthmatic school children and adolescents. This could be due to the difficulty in making asthma diagnosis among preschoolers, which has important implications, for example, less adherence to therapy if physician do not tell parents that their child suffers a chronic condition, which merits a prolonged therapy.

Furthermore, asthma in early childhood is frequently underdiagnosed (receiving such inappropriate labels as chronic bronchitis, wheezy bronchitis, reactive airway disease, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections); therefore, many young children do not receive adequate therapy. However, not all wheeze and cough are caused by asthma and caution is needed to avoid giving infants and young children inappropriate prolonged asthma therapy. Episodic or chronic wheeze, cough, and breathlessness also may be seen in other less common conditions, for example, cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, and foreign-body aspiration [7].

In this review, we assess how to make the diagnosis of asthma among infant/preschoolers with recurrent wheezing and propose the use of the Asthma Predictive Index (API) to identify them.

Diagnosis of asthma in children under 4 years of age

Unfortunately, infants that wheeze and eventually develop 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 yet to determine which young children with recurrent wheezing will develop asthma [8]. Invasive (e.g. bronchoscopy) or noninvasive techniques to measure airway inflammation (e.g. exhaled breath condensate) are being tested in longitudinal studies for their efficacy in early diagnosis of asthma [9]. Also, airway responsiveness measures in infants were a contradictory marker for

 DOI:10.1097/ACI.0b013e3283464c4a

asthma at school age [10,11]. Therefore, diagnosis and management of asthma in young children are primarily based on subjective clinical features and findings from medical examinations.

However, wheezing in the first 3 years of life was a poor predictor of subsequent asthma; instead, atopy in early life predicted future airway disease [12,13]. Similarly, in the Multicentre Allergy Study (MAS) birth cohort study, atopy in parents and immunoglobulin E (IgE) sensitization to common allergens, increased total IgE, and exposure to high levels of indoor allergens in the first 3 years of life were associated with wheezing at the age of 13 years [14]. In contrast, risk for transient wheezing during the first 3 years of life among children that did not wheeze by school age included low baseline levels of lung function, maternal smoking during pregnancy, and lower maternal age [4].

Clinical indices for early predicting asthma

In 2000, the API was developed 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 to predict asthma at school age (15 years). A 'positive' stringent API index requires recurrent episodes of wheezing ($\geq$3 episodes/year) during the first 3 years of age and one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia $\geq$4%). A positive 'loose' index requires less than three episodes of wheezing per year and one of the major or two of the minor criteria (Table 1) [15]. The most used score is the stringent API. A positive stringent API score by the age of 3 years was associated with a 77% chance of active asthma from aged 6–13 years; children with a negative API score at the age of 3 years had less than a 3% chance of developing active asthma during their school years. It is important to clarify that the including criteria for the stringent API was infant/preschoolers with recurrent wheezing ($\geq$3 episodes/year) and the outcome was doctor diagnosis of asthma at age 6 years or more than three episodes of asthma in the last year; and not as was erroneously interpreted by Brand [16], 'the API predicts was developed to predict which of these preschool ever wheezers would have persistent wheeze by the age of 6'.

Table 1 Asthma Predictive Index[a]

Major criteria	Minor criteria
Parental MD asthma[b]	MD allergic rhinitis[d]
MD eczema[c]	Wheezing apart from colds
	Eosinophilia ($\geq$4%)

MD, medical diagnosis. Data from [15].
[a] Loose index for the prediction of asthma: early wheezer and at least one of two major criteria or two of three minor criteria. Stringent index for the prediction of asthma: early frequent wheezer and at least one of the two major criteria or two of three minor criteria.
[b] History of a physician diagnosis of asthma.
[c] Physician diagnosis of atopic dermatitis at age 2 or 3 years.
[d] Physician diagnosis of allergic rhinitis at age 2 or 3 years.

Key points

- This review points out the importance of early diagnosis of asthma in young children with recurrent wheezing using the Asthma Predictive Index (API).
- For that propose we compare the API with two other indices developed and establish the advantage of the former index.
- It also describes the use of the API in epidemiological, randomized clinical trials and studies comparing with other biomarkers and lung function measures.

After the API was created, other scores were developed to predict which preschoolers with recurrent wheezing would be asthmatic patients at school age. In 2003, Kurukulaaratchy *et al.* [17] used data from 1456 children in the Isle of Wight birth cohort to devise a scoring system based on four factors: family history of asthma, recurrent chest infections in the second year of life, atopy 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. And in 2009, Caudri *et al.* [18••] developed a clinical scoring system using data from 3963 children the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort in the Netherlands, in which a subgroup of participants were assessed on a yearly basis until the age of 7–8 years. They found that male sex, postterm delivery, parental education, inhaled medication, wheezing frequency, wheezing/dyspnea apart from colds, respiratory infections, and eczema all independently predicted asthma. The authors established a risk score based on these eight clinical parameters (cutoff $\geq$20 as positive value).

These three asthma indices are on the basis of diverse variables and that condition could make the difference of which index would have more success in different population worldwide [19••]. It is possible that recurrent chest infections or respiratory infections included in the Isle of Wight [17] and PIAMA indices [18••], respectively, might be misreported in episodes of recurrent wheezing [20], as definition of respiratory/chest infection might vary among populations. Also, as the relationship between virus-induced wheezing/asthma depends on the virus (e.g. infants who wheeze with rhinovirus infections have a high risk for subsequent development of asthma) and no information about the type of virus was reported in the Isle of Wight [17] and PIAMA [18••] indices, further

research is needed to clarify this issue. In addition, the use of inhaled medication and level of parental education included in PIAMA index [18••] could depend on local public health strategies and social opportunities, respectively. Also, the inclusion of sex in PIAMA [18••] might have some problems because prevalence of asthma among sex varies with age, and also there are sex differences in the experience of asthma-like symptoms, in diagnosis of asthma, and in the use of asthma medications [21].

The following variables: parental asthma, dermatitis, rhinitis, allergic sensitization by skin prick test and eosinophilia included in these indices were also found related to asthma in several studies. For example, it was reported that asthma among participants who were 7–22 years of age was associated with allergic sensitization by a specific IgE during the first 2 years of life only if a positive parental history of asthma was present [22]. A modified API (mAPI) [23], used in a randomized clinical trial (RCT), incorporated allergic sensitization to at least one aeroallergen as a major criteria and allergic sensitization to milk, eggs, or peanuts as a minor criteria, replacing physician-diagnosed allergic rhinitis from the original API. However, as we see later, the API rather than the mAPI, is used to predict asthma in longitudinal studies. It was reported that allergic sensitization to aeroallergens and foods in early life was associated with asthma at school age [24,25]. Recently, after using a mathematical modeling, an MAS study [26] found that specific IgE responses did not reflect a single phenotype of atopy and only atopy to multiple factors at early ages predicted asthma at the age of 8 years [26]. Moreover, a segmentation mathematical model analysis to predict asthma [27] showed that lack of eosinophilia in wheezing infants was a better predictor of remission of wheezing (91% of remission) by the age of 6 years than measurements of allergic sensitization or total serum levels of IgE. Besides, persistent eosinophilia throughout childhood (until the age of 11 years) was associated to the presence of chronic asthma, independently of atopy (positive skin prick test) [28]. Therefore, in most healthcare settings, it is easier, cheaper, and probably more reliable (allergens vary with region) to determine eosinophil counts in blood samples than to determine allergic sensitization using a skin prick test or by measuring specific IgEs. On the contrary, a recent MAS study [29] reported that allergic rhinitis in preschoolers was a predictor of subsequent wheezing onset. Moreover, as study, using the Tasmanian Longitudinal Health Study, on 1320 infants followed until the age of 44 years, showed that childhood eczema and rhinitis in combination predicted the persistence of childhood asthma to adult atopic asthma (Martin PE, personal communication).

There are other important differences among these indices. The API uses a major and minor criteria system, on the basis of a univariate analysis of unselected ethnic mix cohort. The PIAMA index uses a more accurate but complicated approach, with odd ratios for individual predictors determined from multivariate analyses on nonethnic mix select cohort based on allergic screening results. This generates a more laborious score because the different factors have different weights. As we know, scores will be calculated and used by busy clinicians only if they are easy to remember and use or if they come packaged with a clinical information system that has been validated in different populations, and improves patient outcome. Moreover, clinicians are wary about predictive indices that have not been validated in different settings, particularly in their own.

Sensitivity and specificity provide a perspective of the population that often exaggerates the diagnosis and certainty of the test from the level of individual patients. This is overcome by the use of positive and negative predictive values, but these are influenced by the prevalence of asthma in the population studied. The stringent API has the best combination of sensitivity (although it is low), specificity, and predictive values of the indices compared (Table 2) [15,17,18••,19••]. Another way to set cutoff points for diagnosis tests is through analysis

Table 2 Values from the Asthma Predictive Index and Isle of Wight and Prevention and Incidence of Asthma and Mite Allergy Indices

Risk of asthma	Sensitivity	Specificity	Positive predictive value	Negative predictive value	+LR	−LR
API[a]						
At 6–8 years	22	97	77	90	7.3	0.80
At 11–13 years	15	97	47	85	5	0.88
At 6–13 years	16	97	77	68	6.0	0.86
Isle of Wight[b]						
At 10–11 years	10	98	83	64	7.9	0.53
PIAMA[c]						
At 7–8 years	60	76	23	94	2.5	0.91

API, Asthma Predictive Index; LR, likelihood ratio; +LR, positive likelihood ratio (sensitivity/1-specificity); −LR, negative likelihood ratio (1 − sensitivity/specificity); PIAMA, Prevention and Incidence of Asthma and Mite Allergy. Taken from [19••]. Values from the Asthma Predictive Index [15] and Isle of Wight [17] and PIAMA Indices [18••].
[a] Positive stringent index.
[b] Risk score strata = 4.
[c] Cutoff ≥20.

of receiver–operator characteristic curves. Only the PIAMA index includes this type of analysis – determination of API scores does not require it. Another approach to analyze the results (categorical or continuous) of a diagnosis test is to determine the likelihood ratio (LR), which is more relevant in clinical practice. The LRs from the API and the Isle of Wight indices are similar and good enough to apply in general population (Table 2). As was pointed out and in contrast to LRs, predictive values changes according to prevalence of the disease; therefore the example given by Brand [16] of the API utility in a hypothetical setting with higher prevalence of asthma using only predictive value calculations is inadequate because their positive and negative LRs (7.33 and 0.80, respectively) are identical to those given in the original API study in Tucson [15,19••]. Even more in those hypothetical settings the positive predictive value (that also increase) is clinically a more frequent question to resolve.

Applications of Asthma Predictive Index

Among the three asthma predictive indices discussed above, the API is the only one tested in different populations and in independent studies, such as RCT [30,31], epidemiological Colombian study, and in comparison with other biomarkers [32,33] and with lung function [34•]. In a Colombian epidemiological study, 130 infants were recruited (mean age of 27.2 ± 5.9 months) and follow-up to 5–6 years of age. The stringent API yielded a sensitivity of 43% and specificity of 79% (Rodríguez-Martinez C, personal communication). Recently, a prospective cohort study [32] of 391 young children done in Switzerland (aged 3–47 months) showed that wheezy young children with a stringent API have elevated levels of FeNO compared with children with recurrent wheeze and a loose API or children with recurrent cough. Finally, a study of 91 infants (mean age of 12.05 ± 5.5 months) done in Argentina and Spain showed that those infants with a positive stringent API had significantly lower pulmonary function than those with negative API [34•], speculating that maybe those 'persistent wheezing' infants who were born with a normal lung function and experimented fall in lung function in the first years of life would correspond to this group of children with positive stringent API. And as it was previously demonstrated, low lung function during the first months of life is associated with an increased prevalence of asthma in late childhood [35,36].

Even though, the original goal of the API was to identify subgroups of preschoolers with recurrent wheezing who were at great risk for developing asthma later in life, the major asthma guidelines, such as the international Global Initiative for Asthma [37] and the American guideline [7], now recommend using the stringent API in deciding whether to initiate controller therapy in children that wheeze at the ages of 0–4 years. Healthcare providers are encouraged to begin controller therapy if a child has experienced at least four episodes of wheezing in the past year and has a positive stringent API score, or if a child has at least two exacerbations that require treatment with systemic corticosteroids in a 6-month period. These recommendations will likely decrease morbidity in the preschool-age group, but will not modify the natural course of the asthma; this was demonstrated in an RCT of 285 children aged 2–3 years with positive mAPI score who were treated with fluticasone for two consecutive years [30]. Also, a recent RCT [31] of 238 children, 12–59 months old, with moderate to severe intermittent wheezing and a positive mAPI score, showed benefits from short-term therapy with wet nebulized budesonide or oral montelukast, but among children with a negative mAPI score, neither treatment led to significant improvements (it might be due, in part, to smaller sample sizes). Therefore more RCT need to be done among children with positive and negative API scores in order to compare the efficacy of different controller therapies. As we know, not all children that wheeze have asthma; however, the term asthma, without any qualification or definition, has begun to hinder rather than facilitate progress in the management of wheezy children [38]. This is particularly relevant to children in preschool years, when wheezing syndromes are especially common, and no objective reliable test exists to assist physicians in diagnosing asthma and establishing an appropriate prolong therapy.

Conclusion

Considering the multiple causes of wheezing among preschoolers and the heterogeneity of childhood asthma, it might be impossible to develop a more accurate predictive model without increasing the number of variable factors (i.e. genetic polymorphisms, environmental, socioeconomic, sex, ethnicity, and family health beliefs) that might be taken into account [20]. Even if an index is accurate, to be used by busy clinicians, it must be easy to apply, validated in different populations, and shown to improve patient outcome. The simplicity and reasonable good LRs of the stringent API [15] should allow its potential use for early asthma diagnosis among young children with recurrent wheeze in clinical practice in diverse healthcare settings. More studies need to be done in different populations using the stringent API to reaffirm its utility.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 269).

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