



Identification of infants and preschool children at risk for asthma: predictive scores and biomarkers

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Purpose of review

Predictive asthma scores and biomarkers are important tools that help many physicians in the identification of infants and preschool children at high risk for asthma. Our objective was to review recent data regarding this subject.

Recent findings

Recently, two new predictive asthma scores were developed with some innovative features, such as the definition of scales of asthma risk. In a systematic review, 12 asthma-predictive models were identified with heterogeneous performance. Prospective studies have shown that elevated fractional concentration of nitric oxide (FeNO) is a strong risk factor for latter asthma among early wheezers, and a predictive asthma score with FeNO values has been proposed. Plasma cytokines and exhaled volatile organic compounds were also identified as potential asthma predictors.

Summary

Predictive scores are simple, practical, and inexpensive tools to identify children at high risk for asthma at school age. Whereas some scores are better at identifying asthmatic children, others are better at excluding the diagnosis of asthma. Although promising, clear evidence for FeNO as a robust asthma predictor in comparison to clinical scores is still lacking. Specific IgE and eosinophil counts remain the most consistent biomarkers for the identification of children at risk for asthma, and further studies are necessary to clarify the role of other biomarkers.

Keywords

asthma, biomarkers, children, exhaled nitric oxide, predictive scores

INTRODUCTION

The burden of childhood asthma is substantial. Asthma is one of the most common chronic diseases of childhood, affecting one in every four or five school children in several countries [1]. Although asthma prevalence is declining in some parts of the world, it continues to rise in several others such as USA, Latin America, and Africa [1,2]. Emergency department visits and hospital admissions remain common worldwide in children with asthma, and many deaths still occur.

In developed countries, about one-third of preschool children will wheeze in the first 3 years of life [3]. Preschool wheeze seems to be even higher in other parts of the world, with 40% of infants in Latin America experiencing wheeze in the first year of life and 16% having recurrent wheeze, defined as three or more wheezing episodes [4].

Preschool wheeze is a heterogeneous condition, as wheeze is the common expression of multiple disorders. Approximately two-thirds of preschool

wheezers will stop wheezing at school age [3], making the diagnosis of asthma among preschool children challenging, because there are no widely accepted criteria or currently available accurate tests for the diagnosis of asthma at this age.

Early identification of children at highest risk for asthma would be highly desirable. The identification of asthma at preschool age could allow the prompt introduction of treatment, the selection of patients to recommend environmental interventions, as well as the definition of a closer follow-up. Whereas early initiation of anti-inflammatory

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KEY POINTS

- Predictive scores are simple, practical, and inexpensive tools used to identify children at high risk for asthma at school age, but their performance is heterogeneous, and whereas some scores are better at identifying children at risk for asthma, others are better at identifying those at lowest risk.
- Recently, two new predictive asthma scores have been developed among clinically relevant populations with some innovative features, such as the definition of scales of asthma risk.
- Prospective studies have shown that elevated FeNO in wheezing infants and preschool children is a strong risk factor for later asthma.
- Exhaled volatile organic compounds and plasma cytokines have been identified as predictors of school-age asthma in prospective studies.
- Specific IgE and eosinophil counts remain the most consistent biomarkers for the identification of infants and preschool children at high risk for asthma.

treatment has not demonstrated to alter the natural history of asthma in early life, it was successful in controlling the disease, reducing symptoms and exacerbations [5]. On the contrary, accurate identification of children at lowest risk of asthma would avoid costs and side effects related to treatment.

The utility of predictive scores and biomarkers to identify infants and preschool children at highest risk of subsequent asthma has received significant attention recently, and our objective was to review recent data and information regarding this subject.

PREDICTIVE SCORES

Several predictive scores have been developed in the past two decades to aid in the identification of young children at risk for asthma. They are simple, practical, and inexpensive tools that identify and combine relevant clinical risk factors such as parental history of asthma, eczema, and wheeze without colds. Simple laboratory data, such as eosinophil counts or indicators of allergic sensitization, are employed by some of these tools. Important differences can be observed between these scores regarding the population in which they were developed (high-risk children vs. general population), age (infants vs. preschool children), complexity, and outcomes, such as the definition of asthma and the children's age at the end of follow-up.

The Asthma Predictive Index (API) was developed in 2000 using data from the Tucson Children's Respiratory Study cohort – an unselected general

cohort of 1246 infants [6]. The stringent API is defined by the presence of one major criterion (parental asthma or eczema) or by two minor criteria (allergic rhinitis, wheezing apart from colds or eosinophilia $\geq 4\%$), in combination with frequent episodes of wheezing (≥ 3 episodes in the past 12 months) [6]. For the stringent index, positive predictive value (PPV) of 48% and negative predictive value (NPV) of 92% were found for the diagnosis of asthma at 6 years of age [6]. The API was probably the first tool globally used to identify small children at high risk for asthma and has been employed in clinical trials and recommended by international guidelines [7–9].

Four years later, in 2004, a modified API (mAPI) was used to select high-risk toddlers for the Prevention of Early Asthma in Kids (PEAK) trial [10]. This modification included at least four wheezing exacerbations in a year, added allergic sensitization to aeroallergen(s) as a major criterion and allergic sensitization to foods (milk, egg, or peanuts) as a minor criterion, in place of allergic rhinitis [10]. Recently, the ability of the mAPI to predict asthma at the age of 6, 8, and 11 years was evaluated [11]. This post-hoc analysis was performed in a total of 289 children from the high-risk Childhood Origins of ASThma (COAST) cohort [11]. Sensitivity, specificity, and positive (LR⁺) and negative (LR⁻) likelihood ratios were calculated from years 1, 2, and 3. The mAPI showed very high specificity values (98–100%) and good LR⁺ (4.9–55), but with very low sensitivity (8.2–19%) and high LR⁻ (0.82–0.93) [11]. Interestingly, the authors of this validation study reported the performance of the mAPI in a hypothetical high-risk population (30% pretest probability). Positive post-test probabilities were high, and increased from a positive mAPI at 1 year of 73% to a positive mAPI at 3 years of 90% (asthma diagnosis at 6 years of age). Negative post-test probabilities, however, were approximately 28% for most of the outcomes and very similar to the pretest probabilities, indicating that a positive mAPI was much more clinically useful than a negative one.

Recently, two new predictive scores have been developed – the Asthma Prediction Tool (APT) and the Clinical Asthma Prediction Score (CAPS) [12^{••}, 13^{••}]. These two new scores have substantial similarities. Both scores evaluated asthma risk only among clinically relevant populations, children with recurrent respiratory symptoms, and previous medical visits. The two studies [12^{••}, 13^{••}] also had particular caution in the definition of asthma at school age, selecting more stringent criteria that included not only symptoms but also asthma medication use and/or objective parameters. Finally, instead of a dichotomous outcome (i.e. asthma

present or absent), both scores provide a wider range of probabilities such as low, medium, and high risk.

Pescatore *et al.* [12[■]] developed a clinical score (APT) intended to be used in primary care, which considers only predictive factors easily assessed during a consultation and with no need for any laboratory test. Children aged 1–3 years with parent-reported wheeze or chronic cough (defined as cough without colds or at night) and with at least one medical visit in the past year were selected from a population-based childhood cohort in the United Kingdom. The diagnosis of asthma was determined 5 years later, at the age of 6–8 years, by the combination of current wheeze and use of asthma medication in the past year. Penalized logistic regression analysis was used to identify potential predictors. Complete information was obtained from 1226 of the 2444 children eligible for the study. The overall prevalence of asthma was 28%. Ten predictors remained in the final model and the total score ranged from 0 to 15 points (Table 1) [12[■]].

In the APT, the risk of asthma was divided into three levels: low risk (≤ 5 points), medium risk (6–9 points), and high risk (≥ 10 points). The percentage of children with asthma at the follow-up was 16% among those with low risk, 48% among those with medium risk, and 79% among those with high risk. Sensitivity and specificity for the cut-off points of 5 and 10 were, respectively, 72 and 71% and 22 and 98% [12[■]].

The CAPS score was developed in the Netherlands. Children aged 1–5 years were selected from a prospective cohort who presented to a primary care clinic in the past 12 months due to recurrent coughing (≥ 2 visits), wheezing (≥ 1 visit), and/or shortness of breath (≥ 1 visit) [13[■]]. Clinical information, and total and allergen-specific IgE (cat, dog, and house dust mites) levels were recorded. The diagnosis of asthma was established at age 6 years according to the following criteria: persistent symptoms of asthma and/or use of asthma medication in the past 12 months combined with bronchial hyper-responsiveness (methacholine PC₂₀ < 8.0 mg/ml) or reversibility ($> 10\%$ increase in FEV₁) [13[■]].

Complete information was obtained from 438 children (57% of the total), and the prevalence of asthma at 6 years was 42.7%. The final model comprised five predictors, and the total CAPS score ranged from 0 to 11 points, as shown in Table 2 [13[■]]. According to two predefined thresholds of asthma probabilities (30 and 60%), three ranges of the CAPS score were found: low risk (≤ 3), intermediate risk (4–7), and high risk (≥ 8). The authors advocated that low or high CAPS scores would be most clinically relevant, guiding physicians to apply a

Table 1. The Asthma Prediction Tool

Asthma Prediction Tool	Points
Child's sex	Female (0) Male (1)
Age of the children (years)	1 (0) 2 or 3 (1)
Wheezing or whistling in the chest without cold or flu in the past 12 months	No (0) Yes (1)
Number of wheeze attacks in the past 12 months	0–3 (0) >3 (2)
Interference with daily activities in the past 12 months	No (0) A little (1) A lot (2)
Short of breath during wheezing attacks	Never (0) Sometimes (1) Always (2)
Wheezing or coughing during exercise, laughing, crying, or excitement in the past 12 months	No (0) Yes (1)
Wheezing or coughing due to exposure to dust, grass, pets, or other animals in the past 12 months	No (0) Yes (1)
Eczema in the child	No (0) Yes (1)
Parents with wheezing, asthma, or bronchitis	None (0) Mother (1) Father (1)
Total score (0–15)	

The scores are given in parentheses.
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wait-and-see policy or to introduce asthma treatment [13[■]].

The APT and CAPS scores have limitations. In both studies, high dropout rates were observed. The external validity of these scores in different populations is unknown. The clinical utility of scores in children classified as medium or intermediate risk is uncertain, with 23% of children in APT at medium risk and almost 58% in the CAPS study at intermediate risk [12[■], 13[■]].

A recent systematic review identified 12 prediction models for school-age asthma [14[■]]. Demographic characteristics (sex, age), respiratory symptoms, family history of asthma/allergy, and personal allergic diseases (eczema, rhinitis) were the most common predictors in the models. All studies were rated as having moderate or high risk of bias due to missing data (10 studies) or incomplete information about sample flow (2 studies). Performance of the models was heterogeneous and, in general, models with high LR⁺ also had high LR[−], indicating that some were better at predicting asthma, whereas others were better at ruling out

Table 2. The Clinical Asthma Prediction Score

Clinical Asthma Prediction Score	Categories	Points
Age	1–2 years	0
	2–3 years	1
	3–4 years	2
	4–5 years	3
	5 or more years	4
sIgE	Negative	0
	Positive	2
Parents or siblings with asthma/allergy	Negative	0
	Positive	1
Wheezing-induced sleep disturbances	No	0
	Yes	2
Wheezing without cold	No	0
	Yes	2
Total score (0–11)		

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asthma [14²¹]. These models were derived from Europe and the USA, with none from underdeveloped countries. Environmental exposure and clinical response to asthma treatment – two potentially relevant factors – were not considered in any model [14²¹].

These studies demonstrate that predictive scores are simple, practical, and inexpensive tools that can be used to identify children at high risk for asthma at school age. The overall performance of these scores is variable, as some scores are better at identifying children at risk for asthma, whereas others are better at identifying those at lowest risk.

BIOMARKERS

As clinical parameters alone are not entirely able to identify infants or preschool children whose wheezing will persist or will have current asthma at school age, several biomarkers have been studied as possible predictors of asthma [15²²]. Recent data regarding some of the most studied noninvasive biomarkers are described below.

Exhaled nitric oxide (FeNO)

Fractional concentration of nitric oxide (FeNO) in exhaled air is a noninvasive reflective marker of eosinophilic airway inflammation and is the most studied and used biomarker of exhaled breath [15²²]. FeNO measurement in preschool children and infants is not as well standardized as in older children, and a variety of measurement techniques have been developed [16].

Cross-sectional studies [17–19] in wheezing infants and preschool children have found higher levels of FeNO among those with persistent symptoms, major risk factors for asthma (mainly atopy), and positive predictive scores. Although significant differences in FeNO were found between these groups, marked overlap of FeNO values can be observed and no cut-off could be established.

Prospective studies on the predictive value of FeNO measurements in infants and preschool children for school-age asthma are limited. Elliott *et al.* [20²³] evaluated the capacity of FeNO to predict persistent wheezing in a group of 42 infants and toddlers with recurrent wheezing. Lung function [raised volume rapid thoracic compression technique (RVRTC)] and FeNO were measured at the beginning of the study (6–24 months of age) and at the age of 3 years. Two different techniques of sampling FeNO were employed: during tidal breathing (tidal-FeNO) and during the RVRTC maneuvers [single-breath flow-regulated (SB-FeNO)]. SB-FeNO values (but not tidal-FeNO) at baseline were higher among persistent wheezers (35 vs. 19 ppb; $P < 0.001$). For every 10-ppb increase in baseline SB-FeNO, there was an increase of three times in the odds of persistence of wheezing, and SB-FeNO values over 30 ppb predicted persistent wheezing better than all other predictors, including the API (sensitivity of 77%, specificity of 94%, and AUC of 0.86) [20²³]. Despite these promising findings, measuring SB-FeNO requires complex and expensive equipment, well trained staff, and patient sedation. Tidal-FeNO is more easily measured, but was not a reliable predictor in this study [20²³].

In a prospective study, Singer *et al.* [21²⁴] evaluated the predictive value of FeNO in infants and preschool children. Offline tidal breathing FeNO was measured at baseline (3 months to 4 years of age) and the diagnosis of asthma was defined at school age (6–10 years of age). Higher values of baseline FeNO were found among subsequent asthmatic patients (10.5 vs. 6.2 ppb; $P < 0.001$) and higher FeNO values were associated with an increased odds for asthma of 2.5 [95% confidence interval (CI) 1.5–4.3] [21²⁴].

In this study [21²⁴], a ‘new API’ was proposed, with FeNO higher than 10 ppb as an additional major criterion and removing eosinophilia as a minor criterion, as shown in Table 3.

The new API was proposed as an alternative predictive index that would not require blood sampling. The performance of the new API was similar to the classical API as a predictor of asthma in the whole group of children, with PPV and NPV, respectively, of 58 and 78% vs. 60 and 73% [21²⁴]. FeNO values are particularly sensitive to inhaled

Table 3. The 'New Asthma Predictive Index' [21[¶]]

New Asthma Predictive Index	
Major criteria	Minor criteria
Parents with asthma	Wheezing without cold
Eczema	Allergic rhinitis
FeNO >10ppb	

Stringent index: frequent wheezing (≥ 3 attacks in the last 12 months) + 1 major or 2 minor criteria.

corticosteroid (ICS) use, and in the subgroup of naïve ICS children, the new API performance was better (PPV 68%, NPV 86%) [21[¶]].

The roles of FeNO, interrupter resistance (R_{int}), and specific IgE (sIgE) at the age of 4 years as predictors of asthma symptoms up to the age of 8 were evaluated in a subgroup of symptomatic children from the PIAMA birth cohort [22]. Higher FeNO values at 4 years were significantly associated with wheezing and ICS use between the ages of 5 and 8 years. Each interquartile increase in logFeNO results in 2.1 increase in the odds ratio for wheezing at 8 years [22]. Similar results were found for sIgE (independently from FeNO), but not for R_{int} [22]. Taken in aggregate, these prospective studies have shown that elevated FeNO in wheezing infants and preschool children is a strong risk factor for later asthma.

Exhaled breath condensate

Exhaled breath condensate (EBC) is a simple and noninvasive method to study airway pathophysiology and analyze inflammatory mediators. A recent article reviewed evidence regarding EBC in children with asthma [23]. Methodological issues as differences in sampling protocols and devices and in technical aspects of the assays for EBC biomarkers hampered more direct comparisons. Nevertheless, cross-sectional studies have consistently documented elevated levels of oxides of nitrogen, eicosanoids, and Th2 interleukins, as well as lower pH values in asthmatic patients when compared with healthy controls [23]. EBC pH values were found to discriminate subgroups of preschool children with recurrent wheezing, with significantly lower values among those with allergic sensitization or during acute episodes [24]. Considering recurrent wheezing with allergic sensitization as a proxy for asthma, these authors reported better performance of the API when the index was combined with EBC pH values (AUC 0.80 and 0.94) [24].

Klaassen *et al.* [25] prospectively followed up 202 preschool children with recurrent wheezing until 6 years of age. No difference in several

inflammatory EBC biomarkers was found between asthmatic patients and transient wheezers [25]. In this group of preschool children, exhaled volatile organic compounds (VOCs) in combination with gene expression could significantly improve asthma prediction from the API, with AUC of 0.95, PPV of 90%, and NPV of 89% [26[¶]], thus providing further evidence as to the value of exhaled VOCs as potential predictors of school-age asthma.

Biomarkers in the blood

Eosinophils are closely related to allergic airway inflammation in asthma and have been identified as a marker of corticosteroid response [27[¶]]. Blood eosinophilia has been considered a relevant risk factor for school age for many years and has been incorporated by some predictive models, including the API [6]. A recent comprehensive review identified several longitudinal studies in which significant associations between eosinophilia in infants and preschool children, and later development of asthma were found [27[¶]].

Allergen-specific IgE is a classical risk factor for asthma in children and has been identified as a predictor in several prospective studies [22,28,29]. The presence of positive sIgE in infants or preschool children is a criterion for asthma in several models [10,13[¶],28], improving their performance to predict asthma [13[¶],28]. The relationship between early sensitization and subsequent asthma was evaluated in a longitudinal birth cohort of 620 high-risk newborns in Australia [29]. In this study, skin prick testing was performed at 6, 12, and 24 months, and a positive test to house dust mite at age 1 or 2 years was associated to wheeze at age 12 years with an adjusted odds ratio (OR) of 3.3 (95% CI 1.6–6.9) and of 6.4 (95% CI 3.5–11.7). This association was even stronger among those with eczema and early wheezing [29].

It has been suggested that atopy should not be considered as a binary variable for the assessment of asthma risk as more intense atopy (i.e. multiple sensitization, larger wheal sizes) in preschool children is associated with higher risk of asthma [30]. This observation was confirmed in two UK birth cohorts [31]. Multiple atopy phenotypes were identified, and children with early multiple sensitization were at greater risk of asthma, poorer lung function, elevated FeNO, and hospital admissions for asthma [31].

Several plasma cytokines levels were prospectively evaluated as predictors of allergic asthma in a group of 39 early wheezers followed from 3 to 6 years of age [32]. Three inflammatory plasma mediators were significantly elevated in allergic

asthmatic patients when compared with those without allergic asthma: interferon (IFN)- γ -induced protein 10 (IP-10 – CXCL10), thymus and activation-regulated chemokine (TARC – CCL17), and macrophage-derived chemokine (MDC – CCL22). Using specific cut-off levels for each cytokine, elevated OR for allergic asthma were found for all three mediators (higher than 6.0) [32].

While a disease of the airways, biomarkers in the peripheral circulation, including allergen-specific IgE and eosinophil counts, and more recently plasma cytokine levels, are consistent biomarkers for the identification of infants and preschool children at high risk for asthma.

CONCLUSION

The performance of the asthma predictive scores in preschool children has been shown to be heterogeneous, and whereas some scores are better at identifying children at risk for asthma, others are better at identification of low-risk children. It is important to acknowledge the strengths and limitations of each score before employing it. Two recent scores have been developed with some innovative features, such as the definition of levels of asthma risk. Elevated FeNO is a relevant risk factor for asthma and a promising asthma predictor in young children, but requires better standardization in this age range. Clear evidence for FeNO superiority as an asthma predictor in comparison to clinical scores is still lacking. Further studies are necessary to clarify the role of EBC, VOCs, and plasma cytokines in predicting asthma. Specific IgE and eosinophil counts remain the most consistent biomarkers for the identification of infants and preschool children at high risk for asthma.

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Conflicts of interest

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