Published in final edited form as:

Ann Allergy Asthma Immunol. 2014 March ; 112(3): 188–190. doi:10.1016/j.anai.2013.12.001.

Utility of the Asthma Predictive Index in predicting childhood asthma and identifying disease-modifying interventions

Michelle Fox Huffaker, MD^{*,†} and Wanda Phipatanakul, MD, MS^{†,‡}

^{*}Brigham and Women's Hospital, Boston, Massachusetts

[†]Harvard Medical School, Boston, Massachusetts

[‡]Boston Children's Hospital, Boston, Massachusetts

The Asthma Predictive Index (API) was developed by Castro-Rodriguez et al in 2000 to identify children who may develop asthma. The API has since been well validated and internationally supported, although many clinicians remain skeptical about its utility. In this article, we provide support demonstrating that the API is an important clinical tool and address the concerns regarding its shortcomings.

Not all children who wheeze will develop asthma, and yet identifying asthmatic children early may be important in reducing respiratory complications later in life.¹ Most children who develop asthma have other atopic features, including allergic rhinitis, food allergy, or atopic dermatitis. Evidence suggests that children who develop asthma early in life, before the age of 3 years, may develop persistent lung function abnormalities.^{2,3} Controlling symptoms in young children is important to prevent chronic lung function abnormalities, and multiple studies have found that treating associated symptoms may help prevent the development and progression of asthma.^{2–7} Having a tool, such as the API, to determine which children may develop asthma may help clinicians target and treat atopic and asthmatic children before they develop chronic and persistent lung function abnormalities.

Furthermore, no biochemical or other medical test is readily available to determine which children will develop asthma. Children younger than 5 years are too young for spirometry to be reliably performed. Bronchoalveolar lavage is too invasive to be performed routinely for all children who wheeze. IgE is the only biomarker that is readily available, and it is unfortunately affected by age and the results are difficult to interpret in young children; thus, it lacks clinically meaningful sensitivity and specificity.⁸ Fractional excretion of nitric oxide is a potential biomarker, but further research is needed before this can be widely used and interpreted in this population.

The API was created to fill this need for a noninvasive clinical tool to predict the development of asthma in children. In 2000, Castro-Rodriguez et al⁹ examined data from the

Tucson Children's Respiratory Study, a longitudinal study of respiratory illnesses in children, and identified potential predictors of asthma. In this study, parents were surveyed on the frequency of wheezing in their children, and physicians documented the presence or absence of allergic rhinitis, eczema, and eosinophilia, among other atopic measures.⁹ From this information, the authors developed the stringent API and the loose API, 2 simple and inexpensive indexes for asthma prediction (Table 1).⁹

The stringent API has been statistically validated as a clinical tool for asthma predication. Castro-Rodriguez et al⁹ tested the sensitivity, specificity, positive predictive value, and negative predictive value of the API at 6, 8, 11, and 13 years of age and at least one time point when the child had active asthma. The API had modest sensitivity, ranging from 14.8% to 27.5%, but had a very high specificity, consistently greater than 96% across each age group tested. When taking the prevalence of asthma in the study into account, the authors found that the positive predictive value ranges from 42% to 51.5% when tested at specific ages but at any given time point was as high as 76.6%. The negative predictive value was 84.2% to 91.6% when tested at specific ages and 68.3% at any given time point. In this study and subsequent studies, the stringent API outperformed the loose API and thus is the focus of this article (referred to simply as the API).^{9–12}

Independent studies have since validated the use of the API and replicated the findings of Castro-Rodriguez et al in other pediatric populations.^{10,11,13} A small prospective cohort study by Rodriguez-Martinez et al¹¹ examined the API in a group of preschoolers in Colombia and found that again the API yielded a high specificity (79.2%). In a much larger study, a group in the Netherlands examined the API, found it to have specificity up to 92%, and used it as a benchmark by which to compare their own tool, the Prevention and Incidence of Asthma and Mite Allergy risk score.¹⁰ Another large study found similar results in a pediatric population in the United Kingdom, with specificity of 93%.¹² From this internal and external validation and consistently high specificity, we can conclude that a positive API score is a strong predictor of asthma in a child with wheezing. In addition, in further statistical analysis by an independent group, the API was found to have a high positive likelihood ratio, therefore demonstrating that a positive API score can significantly change the posttest probability of a child having asthma and thus significantly alter medical management.¹³

Several major strengths of the API are in the design. The API is a simple set of equally weighted criteria with a binary scoring system: the criteria are either met or not met. This simple scoring system allows easy implementation and interpretation of the API. The criteria are also relatively noninvasive. The peripheral blood draw, which has been cited as a potential limitation to the applicability of the tool, is not always needed.¹³ The scoring system only requires a peripheral blood draw if confirming the presence of peripheral eosinophilia changes the outcome of the score. Given that the score is binary, there is no need for the peripheral blood draw if the score is positive or definitively negative by the noninvasive measurements. Furthermore, the API is dependent on objective rather than subjective measures. The metrics within the API score require physician documentation rather than parental observation. Studies examining parents' definition of asthma symptoms found that parents' perceptions of asthma symptoms were variable and differed from those

of clinicians.¹⁴ The objectivity of the API makes it less subject to cultural differences in presentation and parental reporting. This simple and objective design makes the API readily applicable to everyday practice.

The major limitation of the API is that a negative API score does not significantly change the posttest probability.^{9,13} As mentioned, the sensitivity of the API is modest, and thus it cannot be used to rule out development of asthma.^{9,13} Clinicians must be educated on proper interpretation of the negative API score so as not to disregard signs and symptoms in children who may develop asthma. Further research is needed to understand this population of patients and elucidate defining traits that may allow clinicians to predict who among these children who wheeze will develop asthma. Other groups have since developed other predictive indexes, but none has performed as well, been as simple to implement, or been used as broadly as the API.^{10,13,15,16} In addition, no other scoring system has a high sensitivity, and thus none is useful for ruling out asthma or for use in conjunction with the API.^{10,13,15,16}

A slight variation to the API, the modified API, was developed for the Preventing Early Asthma in Kids clinical trial in 2004. The modified API requires more than 4 episodes of wheezing and replaces allergic rhinitis with sensitization to aeroallergens as a major criterion and sensitivity to milk, eggs, or peanuts as a minor criterion.¹⁷ The modified API was designed based on expert opinion that these subtle changes to the API criteria may improve the objectivity of the scoring system, and several clinical trials have adopted its use.^{4,17,18} A recent prospective study of high-risk pre-school children in the Childhood Origins of Asthma cohort found that a positive modified API similar to a positive API markedly increased posttest probability of a child developing asthma.¹⁸ Further validation of the modified API is needed in larger and more diverse patient populations.

The features used to define a positive API score may allow us to predict response to therapeutic treatment. Several studies have aimed to test whether early interventions targeted toward children with a positive API score or a positive modified API score may help prevent the development and alter the progression of asthma.²⁻⁷ Guilbert et al⁴ reported that treatment of asthma in preschool children with modified API with inhaled corticosteroids decreased exacerbations while the patient was undergoing therapy but did not alter the progression of asthma once inhaled corticosteroids were discontinued. Studies have found differential improvement in asthma severity markers with the use of budesonide or montelukast in children with positive API scores.⁷ Systemic corticosteroids also have promise in reducing duration of exacerbation, specifically in children with a positive API score.⁶

Furthermore, the API uses several atopic traits in its scoring system, and studies have found that a large proportion of children with a positive API score not only have allergic sensitization but also are at risk for developing persistent wheeze.^{4,19} Broad-based environmental interventions demonstrate some benefit but may not be completely effective because of the inability to target all inhalant antigens.²⁰ Although limited as open-label trials, allergen specific immunotherapy prevented the development of asthma up to 7 years later in children with allergic rhinoconjunctivitis, which stresses the importance of allergy

and the API in predicting asthma.⁵ Increasing availability of biologics that interfere with atopy for therapeutic use in young children, such as anti-IgE, anti-interleukin 4, and anti-interleukin 13, may hold promise in altering the progression and course of asthma. The API may therefore be useful in identifying at-risk children who would benefit from early therapeutic interventions, and further research is needed to identify agents that could alter the atopic allergic, asthma march.

In summary, early, untreated asthma may have lifelong consequences, and thus clinicians must try to identify and treat at-risk children. The API is simple, inexpensive, and noninvasive and has been well validated. Clinicians can use a positive API score to identify at-risk children and educate parents on the importance of asthma maintenance therapy and treatment of flares. Like any test, the API must be interpreted and acted on appropriately. Further studies are needed to determine whether appropriate interpretation of the positive API score changes management or outcomes in children who wheeze. The use of the API in conjunction with newer antiallergen therapy holds promise for preventing the development and progression of asthma.

Acknowledgments

Funding: This study was funded by National Institutes of Health/National Institute of Allergy and Infectious Diseases grant AI106822.

References

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: The Group Health Medical Associates. *N Engl J Med.* 1995; 332:133–138. [PubMed: 7800004]
2. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med.* 2005; 172:1253–1258. [PubMed: 16109980]
3. O'Brian AL, Lemanske RF Jr, Evans MD, Gangnon RE, Gern JE, Jackson DJ. Recurrent severe exacerbations in early life and reduced lung function at school age. *J Allergy Clin Immunol.* 2012; 129:1162–1164. [PubMed: 22236729]
4. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med.* 2006; 354:1985–1997. [PubMed: 16687711]
5. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy.* 2007; 62:943–948. [PubMed: 17620073]
6. Jartti T, Lehtinen P, Vanto T, et al. Atopic characteristics of wheezing children and responses to prednisolone. *Pediatr Pulmonol.* 2007; 42:1125–1133. [PubMed: 17968992]
7. Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol.* 2008; 122:1127–1135. [PubMed: 18973936]
8. Wittig HJ, Belloit J, De Fillippi I, Royal G. Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. *J Allergy Clin Immunol.* 1980; 66:305–313. [PubMed: 7419833]
9. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med.* 2000; 162(4 pt 1): 1403–1406. [PubMed: 11029352]

10. Caudri D, Wijga AA, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol.* 2009; 124:903–910. [PubMed: 19665765]
11. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Discriminative properties of two predictive indices for asthma diagnosis in a sample of preschoolers with recurrent wheezing. *Pediatr Pulmonol.* 2011; 46:1175–1181. [PubMed: 21626716]
12. Leonardi NA, Spycher BD, Strippoli MP, Frey U, Silverman M, Kuehni CE. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol.* 2011; 127:1466–1472. [PubMed: 21453960]
13. Fouzas S, Brand PL. Predicting persistence of asthma in preschool wheezers: crystal balls or muddy waters? *Paediatr Respir Rev.* 2013; 14:46–52. [PubMed: 23347660]
14. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by “wheeze”? *Arch Dis Child.* 2000; 82:327–332. [PubMed: 10735844]
15. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *Eur Respir J.* 2003; 22:767–771. [PubMed: 14621083]
16. Devulapalli CS, Carlsen KC, Haland G, et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax.* 2008; 63:8–13. [PubMed: 17615086]
17. Guilbert TW, Morgan WJ, Krawiec M, et al. The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials.* 2004; 25:286–310. [PubMed: 15157730]
18. Chang TS, Lemanske RF Jr, Guilbert TW, et al. Evaluation of the Modified Asthma Predictive Index in High-Risk Preschool Children. *J Allergy Clin Immunol Pract.* 2013; 1(2)
19. Guilbert TW, Morgan WJ, Zeiger RS, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol.* 2004; 114:1282–1287. [PubMed: 15577824]
20. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol.* 2001; 108:732–737. [PubMed: 11692097]

Table 1The Asthma Predictive Index⁹

Stringent API: More than 3 episodes of wheezing per year during the first 3 years of life and 1 major or 2 minor criteria Loose API: Fewer than 3 episodes of wheezing per year and 1 major or 2 minor criteria			
Major Criteria		Minor Criteria	
1	Asthma in a parent, documented by a physician	1	Allergic rhinitis in the child, documented by a physician
2	Eczema in the child, documented by a physician	2	Wheezing apart from colds, reported by the parents
		3	Peripheral eosinophilia greater than or equal to 4%