Editorial

Another Predictive Score for Childhood Asthma: The Search Remains

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

Approximately 40% of all young children have at least 1 episode of asthma-like symptoms.[1] Moreover, approximately 80% of asthmatic patients date their disease onset to the first years of life.[2] Fortunately, only 30% of preschoolers with recurrent wheezing still have asthma at age 6 years.[1] However, knowledge of which infants and preschoolers with recurrent wheezing will have asthma once they reach school age is of clinical importance for the following reasons. First, asthma is one of the most prevalent chronic diseases in childhood; second, the greatest decline in lung function in asthmatic patients occurs during the preschool period[3]; third, asthma-like symptoms are particularly difficult to control in preschool than in later childhood[4]; and fourth, several wheezing phenotypes coexist at preschool age.[1] Therefore, identifying which children with wheeze at a young age will experience asthma at school age will help to better predict the prognosis of early wheezing and respiratory symptoms and also provide rationale for specific treatment and potential prevention strategies. Despite the importance of the above, diagnosis of asthma at an early age remains a challenge for physicians. The development of asthma prediction rules may provide an answer to this challenge.

Four consecutive steps are needed to develop prognostic or diagnostic prediction rules: development, validation/assessment, impact, and implementation.[5] In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Amin et al[6] present the development (the first step) of a new predictive index for *objectively confirmed asthma* at age 7 years using data from the Cincinnati Childhood Allergy and Air Pollution Study, a high-risk prospective birth cohort (children were eligible for enrollment if they had at least 1 parent who was skin prick tested positive to a common aeroallergen). The new Asthma Predictive Index (API) named the "University of Cincinnati API" (ucAPI) is derived and adapted from the original API[7] and modified API (mAPI).[8] A positive ucAPI at age 3 years was defined as having 2 or more episodes of wheezing in the previous 12 months at the third-year clinic visit, and 1 of the 3 major criteria (parental asthma, allergic sensitization to $\geq$1 aeroallergens, or a history of eczema) or 2 of the 3 minor criteria (wheezing without a cold, physician-diagnosed allergic rhinitis, or allergic sensitization to milk or egg). In addition, Amin et al[6] determined the statistical properties of specific persistent wheezing phenotypes at age 3 years (persistent wheezing, atopic persistent wheezing, and nonatopic persistent wheezing) to predict objectively confirmed asthma at age 7 years.

Objectively confirmed asthma was defined as parent-reported or physician-diagnosed asthma confirmed by (1) either a change of 12% or more in FEV_1 postbronchodilator or a positive methacholine challenge ($PC_{20} \leq 4$ mg/mL) or (2) previous treatment with daily asthma controller medication(s). Of the 762 children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study cohort, 589 (77.3%) had complete data at 7 years that were used to analyze the several prediction rules. Both prediction rules of a positive ucAPI and persistent wheezing at age 3 years were significant predictors of objectively confirmed asthma at age 7 years. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (LR), and negative LR of ucAPI were 44%, 94.1%, 60.3%, 89.3%, 7.5, and 0.6, respectively. The values for persistent wheezing were 36%, 95%, 61%, 87%, 7.2, and 0.7, respectively. Using 4 or more wheezing episodes (as used in the mAPI) to define a positive ucAPI, the sensitivity, specificity, positive predictive value, negative predictive value, positive LR, and negative LR were 32%, 96%, 91%, 88%, 7.8, and 0.7, respectively.

After multivariate analysis (covariates were sex, race, exposure to environmental tobacco smoke, breast-feeding, sensitization to aeroallergen, egg and milk sensitization at age 1 and 3 years, cat ownership, and elemental carbon attributable to traffic exposure), the positive ucAPI (using $\geq$2 wheezing episodes) was associated with a significant risk for objectively confirmed asthma at age 7 years (adjusted odds ratio, 13.3; 95% CI, 7-25.2; $P < .01$), as was the persistent wheezing (adjusted odds ratio = 9.8; 95% CI, 4.9-19.2; $P < .01$). The authors concluded that both predictive rules, a positive ucAPI and persistent wheeze at age 3 years, were associated with objectively confirmed asthma at age 7 years; however, the ucAPI evidenced better prediction, suggesting the usefulness of ucAPI as a tool for predicting future asthma in school-age children.

Limitations to the ucAPI exist. First, as noted by the authors, because the ucAPI predictive rule was developed in a high-risk cohort, its findings are limited and cannot be generalized to children without a family history of allergy. Similarly, the mAPI developed by expert opinion for a high-risk cohort[8] was recently validated only in another high-risk birth cohort.[9] Second, although asthma is usually only clinically diagnosed, this is the first study to develop predictive rules based on objectively confirmed asthma. Adenosine challenge was reported as a more specific test for the diagnosis of asthma[10]; therefore, it may have been a better test than the methacholine challenge testing chosen

Departments of Pediatrics & Public Health/Family Medicine, School of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile

Conflicts of interest: JA Castro-Rodriguez has received research support from Novartis; has received lecture fees from AstraZeneca, GlaxoSmithKline, MSD, Novartis, and Sanofi; and has received travel support from AstraZeneca, GlaxoSmithKline, and Novartis.

Received for publication October 14, 2014; accepted for publication October 14, 2014.

Corresponding author: Jose A. Castro-Rodriguez, MD, PhD, Lira 44, 1er. piso, Casilla 114-D, Santiago, Chile. E-mail: jacastro17@hotmail.com.

J Allergy Clin Immunol Pract 2014;2:716-8.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2014.10.007

for the present study. Specifically, the indirect bronchial challenge adenosine challenge test functions by causing the endogenous release of mediators from eosinophils and mast cells, causing airway smooth muscle contraction mimicking clinical asthma.[11] Third, the ucAPI (in contrast to the original API[7]) used a positive skin prick test result to milk and egg instead of eosinophilia as one of the minor criteria. Therefore, it may have lost some of the strengths of eosinophilia to predict persistent wheezing at school age, independently of a positive aeroallergen or food allergen test result.[12,13] In addition, lung function trajectories from birth through age 16 years reflect asthma phenotypes based on allergic dermatitis and rhinitis (as used in the original API criteria), but not driven by allergic sensitization.[14] Because the rate of aeroallergen sensitization is lower during early childhood than during later childhood, allergen sensitization may not be optimal for prediction, particularly because its determination is not routinely obtained during clinical practice.[15]

The LR best reflects the diagnostic accuracy of a test. The positive LRs of different prediction rules reported for assessing the development of asthma at school age include the following: mAPI[9] (LR = 21 for asthma at age 6 years), Isle of Wight score[16] (LR = 7.9 for asthma at age 10-11 years), ucAPI (LR = 7.5 for asthma at age 7 years), original stringent API[7] (LR = 7.4 for asthma at age 6 years), and Prevention and Incidence of Asthma and Mite Allergy risk score of 20 or more[17] (LR = 2.5 for asthma at age 7-8 years). However, several important issues need to be understood about these asthma predictive rules before choosing the optimal rule. Among these 5 prediction rules, only the original API[7] is relatively generalizable because it was developed in an unselected ethnically diverse birth cohort. The PIAMA[17] and Isle of Wight[16] prediction rules include respiratory tract/recurrent chest infections among their many criteria, which could misrepresent the reporting of episodes of recurrent wheezing. The PIAMA[17] prediction rule is more laborious to determine because the many criteria used have different weights; in addition, its generalizability may be reduced because it includes health beliefs and socioeconomic information that may vary between ethnicities. The Isle of Wight[16] and mAPI[9] scores suffer from a lack of external validation (second step of clinical predictive rule). Only the original stringent API[7] and the PIAMA[17] prediction rules were validated in different populations.

Moreover, the original stringent API[7] is the only asthma prediction rule in which the third (impact) and fourth (implementation) steps of clinical prediction rules are indirectly being studied presently. The original stringent API was compared and correlated with surrogate markers of airway inflammation, lung function, and bronchial biopsies. Infants and toddlers with recurrent wheezing and positive API had higher fractional exhaled nitric oxide than did those with negative API.[18,19] Infants and young children with recurrent wheezing and positive API had a significantly lower lung function measured by values of the maximal flow at functional residual capacity at an early age than did those with negative API.[20] And it was reported that a significant difference in the thickness of the basement membrane was seen among preschoolers who later developed a positive API.[21] Adding an exhaled breath condensate pH (a promising new noninvasive technique for assessment of airway inflammation) to the original stringent API results in a lower positive LR (5.88).[22] Fractional exhaled nitric oxide when used as a minor criteria replacing eosinophil determination of the original API showed a lower positive LR (1.99) for predictive asthma at age 4 years.[23] Finally, an implementation or application value of the original API for therapeutic strategies was recently published. It revealed that inhaled corticosteroids and leukotriene receptor antagonists worked equally well among those with negative APIs but that leukotriene receptor antagonists worked better for the positive API group.[24]

Because no accurate screening test using genetic or single biochemical markers has been developed to determine which young children with recurrent wheezing will have asthma at school age, at the present time diagnosis of asthma needs to be based on clinical scores. For clinical use, the original stringent API is simple, inexpensive, and noninvasive and has been well validated.[25] Therefore, clinicians worldwide can use a positive original stringent API to identify at-risk children and educate parents on the importance of asthma maintenance therapy and treatment of flares.[25] Its major strength is its good positive LR (the effect on posttest probability of disease improved significantly), but because its sensitivity is modest it cannot be used to rule out the development of asthma.[25] More studies are needed to explore the effect of asthma controller medications based on a infant's/preschooler's API status.

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8.
2. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964-1983. Am Rev Respir Dis 1992;146:888-94.
3. Kuehni CE, Frey U. Age-related differences in perceived asthma control in childhood: guidelines and reality. Eur Respir J 2002;20:880-9.
4. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, 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;172:1253-8.
5. Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: a review. J Clin Epidemiol 2008;61:1085-94.
6. Amin P, Levin L, Epstein T, Ryan P, Le Masters G, Khurana-Hershey G, et al. Optimum predictors of childhood asthma: persistent wheeze or the asthma predictive index? J Allergy Clin Immunol Pract 2014;2:709-15.
7. 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;162:1403-6.
8. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefler SJ, et al. Prevention of Early Asthma in Kids Study, Childhood Asthma Research and Education Network. 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.
9. Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. J Allergy Clin Immunol Pract 2013;1:152-6.
10. Avital A, Springer C, Bar-Yishay E, Godfrey S. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. Thorax 1995;50:511-6.
11. Ater D, Bar BE, Fireman N, Fireman E, Shai H, Tasher D, et al. Asthma-predictive-index, bronchial-challenge, sputum eosinophils in acutely wheezing preschoolers. Pediatr Pulmonol 2014;49:952-9.
12. Just J, Nicoloyanis N, Chauvin M, Pribil C, Grimfeld A, Duru G. Lack of eosinophilia can predict remission in wheezy infants? Clin Exp Allergy 2008;38:767-73.
13. Karakoc F, Remes ST, Martinez FD, Wright AL. The association between persistent eosinophilia and asthma in childhood is independent of atopic status. Clin Exp Allergy 2002;32:51-6.
14. Lødrup Carlsen KC, Mowinckel P, Hovland V, Håland G, Riiser A, Carlsen KH. Lung function trajectories from birth through puberty reflect asthma phenotypes with allergic comorbidity. J Allergy Clin Immunol 2014;4:917-23.e7.

15. Sahiner UM, Buyuktiryaki AB, Yavuz ST, Yilmaz EA, Cavkaytar O, Tuncer A, et al. The spectrum of aeroallergen sensitization in children diagnosed with asthma during first 2 years of life. Allergy Asthma Proc 2013;34:356-61.
16. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. Eur Respir J 2003;22:767-71.
17. Caudri D, Wijga A, A Schipper CM, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. J Allergy Clin Immunol 2009;124:903-10.e1-7.
18. Balinotti JE, Colom A, Kofman C, Teper A. Association between the Asthma Predictive Index and levels of exhaled nitric oxide in infants and toddlers with recurrent wheezing. Arch Argent Pediatr 2013;111:191-5.
19. Castro-Rodriguez JA, Sardón O, Pérez-Yarza EG, Korta J, Aldasoro A, Corcuera P, et al. Young infants with recurrent wheezing and positive asthma predictive index have higher levels of exhaled nitric oxide. J Asthma 2013;50:162-5.
20. Keklikian E, Sanchez-Solis M, Bonina AJ, Meneguzzi A, Pastor-Vivero MD, Mondejar-Lopez P, et al. Do risk factors for persistent asthma modify lung function in infants and young children with recurrent wheeze? Pediatr Pulmonol 2010;45:914-8.
21. Berankova K, Uhlik J, Honkova L, Pohunek P. Structural changes in the bronchial mucosa of young children at risk of developing asthma. Pediatr Allergy Immunol 2014;25:136-42.
22. von Jagwitz M, Pessler F, Akmatov M, Li J, Range U, Vogelberg C. Reduced breath condensate pH in asymptomatic children with prior wheezing as a risk factor for asthma. J Allergy Clin Immunol 2011;128:50-5.
23. Singer F, Luchsinger I, Inci D, Knauer N, Latzin P, Wildhaber JH, et al. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. Allergy 2013;68:531-8.
24. Li YQ, Xue HY, Chen W, Cao LF. Application of asthma predictive index-based group therapy in wheezing children under 5 years of age [in Chinese]. Zhongguo Dang Dai Er Ke Za Zhi 2014;16:795-9.
25. Huffaker MF, Phipatanakul W. Utility of the Asthma Predictive Index in predicting childhood asthma and identifying disease-modifying interventions. Ann Allergy Asthma Immunol 2014;112:188-90.