

Respiratory symptoms in asthma: The view through a wide-angle lens

Elizabeth C. Matsui, MD *Baltimore, Md*

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In this issue of the *Journal*, 2 articles address the broad question of the clinical relevance of nonwheezing respiratory symptoms in 2 different populations: children with established asthma¹ and children at risk for asthma.² Bisgaard et al¹ performed a secondary analysis of data collected in the context of a clinical trial of preschool-aged children with asthma and examined wheeze, cough, and difficulty breathing as predictors of exacerbations. The authors found that any combination of symptoms that included cough was a more sensitive predictor of an exacerbation the following day than combinations of symptoms including either wheeze or difficulty breathing and that half of the exacerbations were not preceded by parent-reported wheeze. The authors conclude that the more narrowly focused approach of relying on wheeze as the sole symptom informing treatment could lead to delayed treatment or undertreatment of exacerbations, which could be avoided by taking a broader view, and relying on a global assessment of “significant troublesome lung symptoms” instead.

On the one hand, this finding reflects standard clinical care as described in both US³ and international⁴ asthma guidelines, which incorporate evaluation of nonwheezing symptoms as an integral part of the assessment of asthma control. Validated asthma symptom and control tools also include assessment of nonwheezing asthma symptoms.^{5,6} On the other hand, clinical practice guidelines focus less on identification of an imminent exacerbation, and this study’s findings suggest that educating parents and clinicians specifically that “significant troublesome lung symptoms,” even when wheeze is not present, are a potential harbinger of an exacerbation could result in earlier intervention and potential reduction of morbidity. This hypothesis, that intervention at the onset of significant lower respiratory tract symptoms could reduce morbidity, is ripe for testing in a clinical trial.

It is important to note that although wheeze was a significantly less sensitive indicator of an impending exacerbation than nonwheezing symptoms, wheeze was a more specific indicator of an impending exacerbation, highlighting the fact that, despite its well-described limitations, wheeze is still an important asthma symptom and should not be dismissed by a clinician or tossed aside in the development of practice guidelines or asthma assessment tools, particularly in populations in which wheeze is

a common term. Clinical experience would suggest that the authors’ observations reflect the natural history of asthma exacerbations, which typically begin with milder nonwheezing symptoms and then progress to frank wheezing. Consistent with this observation, others have reported that nonwheezing symptoms are the most reliable predictor of subsequent wheeze in young children, with significant cough having a 74% positive predictive value for subsequent wheezing.⁷ Furthermore, parents might not attribute nonwheezing symptoms to asthma. When parents report that their asthmatic child has a cough, they often add that “it’s because he has a cold,” not recognizing that the cough is likely attributable to their child’s asthma and a potential reason to intervene.

Several questions remain. For example, are nonwheezing symptoms a sufficiently accurate predictor of an exacerbation that their occurrence should trigger a step-up in therapy? And because nonwheezing symptoms most strongly predicted an exacerbation occurring the following day, is this 1-day lead time a sufficient amount of time for an intervention to avert an exacerbation? Oral corticosteroids would be expected to take effect in this time period, but a step-up in controller medication would not. Although the symptom diary used in the study captured symptoms attributable to asthma so that the parents in the study were presumably aware that the nonwheezing symptoms were asthma related, it is worth understanding how often nonwheezing respiratory symptoms are unrecognized as asthma related because this might be an important opportunity for educational intervention. Lastly, whether the findings reported by Bisgaard et al¹ are applicable to other populations, such as school-aged children, adolescents, or adults, is unclear and deserves further study.

In the second article Skytt et al² examined the relationship between recurrent troublesome breathing problems in the first 3 years of life and asthma at school age. The authors focused on episodes of troublesome lung symptoms, which were defined as at least 3 days of respiratory symptoms that severely affected the child’s breathing but were not caused by pneumonia or pseudocroup. A diagnosis of pneumonia or pseudocroup was made by a study physician on the basis of physical examination findings. A study physician also determined whether the participant was wheezing. The authors found that the risk of asthma at school age increased with each additional episode of troublesome lung symptoms. More importantly, this association was present even among children who never wheezed, indicating that preschool-aged children with significant recurrent nonwheezing symptoms are at increased risk for asthma. This finding points to the importance of including an assessment of nonwheezing respiratory symptoms in future cohorts to develop a broader and perhaps more accurate view of the natural history of asthma.

Previous population-based cohort studies have focused less on the role of nonwheezing respiratory symptoms during early

From the Department of Pediatrics, Johns Hopkins University.

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Corresponding author: Elizabeth C. Matsui, MD, Department of Pediatrics, Johns Hopkins University, 600 North Wolfe St, CMSC 1102, Baltimore, MD 21287. E-mail: ematsui@jhmi.edu.

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childhood in predicting the risk of asthma at school age. For example, although the Tucson Children's Respiratory Study made some seminal observations about the natural history of recurrent wheeze in early childhood, nonwheezing symptoms were not a focus of this cohort.⁸ However, an Australian childhood cohort did evaluate both recurrent wheeze and chronic cough as predictors of continued symptoms at school age.⁹ The authors reported that children with chronic cough were less atopic and had better lung function than children with recurrent wheezing. Preschool-aged children with chronic cough were also unlikely to wheeze at school age, but more than a third of them went on to have chronic cough at school age. However, whether the children with chronic cough at school age had asthma is unknown. Taking this previous work and the article by Skytt et al² into consideration, it is tempting to speculate that children with significant nonwheezing respiratory symptoms represent a phenotype of asthma distinct from the wheezing phenotype. To that end, it would be interesting to know whether the preschool-aged children with predominantly nonwheezing respiratory symptoms were similar to children with predominantly wheeze with respect to atopy, lung function, and other features of asthma.

Although Skytt et al² demonstrate that significant recurrent nonwheezing symptoms are predictive of asthma at school age, how this phenotype compares with recurrent wheeze in predicting asthma is not clear. It is possible, for example, that recurrent wheeze is a more specific indicator for asthma at school age, but this question remains unanswered because wheezing episodes were not compared with nonwheezing episodes. Another important caveat is that more than 25% of initial episodes of troublesome respiratory symptoms identified by parents were attributed to pneumonia or pseudocroup, so that identification of preschool-aged children with recurrent nonwheezing respiratory symptoms could not be based on parental report alone.

Although wheeze remains a relevant asthma-related symptom in many populations, these 2 articles underscore the importance of taking a broader view of respiratory symptoms rather than focusing on wheeze alone. Nonwheezing respiratory symptoms should be evaluated further as a predictor of an imminent exacerbation in preschool-aged asthmatic patients and as a marker for preschool-aged children at higher risk of having asthma at school age. These studies also serve to underscore the importance of educating parents of asthmatic patients about nonwheezing respiratory symptoms and their importance as a barometer of asthma control and a potential sign of a brewing exacerbation.

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