

Does exhaled nitric oxide measurement help distinguish between wheezing phenotypes in preschool children?

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The occurrence of several wheezing phenotypes during the preschool years, with their differing prognoses, adds complexity to the clinical evaluation and management of the young wheezing child. The Tucson Children's Respiratory Study has elegantly demonstrated the existence of at least 3 wheezing phenotypes in preschool children¹ and recently confirmed that the patterns of wheezing observed during the first 6 years of life tend to persist through adolescence.² However, given the high prevalence of wheezing in this age group and to optimize care of this population, early identification of the child at highest risk for persistence of wheezing would seem desirable. Based on the Tucson Children's Respiratory Study, Castro-Rodriguez et al³ constructed an asthma predictive index, which allows clinicians to categorize children with recurrent wheezing at either high or low risk for active asthma during the school years. This classification is based on the presence of recurrent wheezing and risk factors, including either 1 major risk factor (personal eczema or parental asthma) or 2 minor risk factors (peripheral blood eosinophilia $\geq 4\%$, wheezing unrelated to infections, or physician-diagnosed allergic rhinitis). Children with a stringent index (early frequent wheezing during the first 3 years plus 1 major or 2 minor risk factors) were 9.8 times more likely to experience active asthma at 6 years of age than children with a negative index, whereas children with a loose index (early wheezing during the first 3 years of life plus 1 major or 2 minor risk factors) were 5.5 times more likely to experience active asthma at 6 years of age than children with a negative index.

The measurement of the fractional concentration of exhaled nitric oxide (FE_{NO}) has received much interest for its ability to noninvasively measure eosinophilic airway inflammation.⁴ Levels of FE_{NO} have been demonstrated, in older children, to be related to several features of atopy and asthma, including peripheral blood eosinophilia and airway hyperresponsiveness.⁵ FE_{NO} has been studied in preschool children for its ability to distinguish between children with asthma and those without, as well as being a predictor of respiratory symptoms during early childhood. Brussee et al⁶

examined FE_{NO} in a birth cohort including high-risk (maternal atopy) and low-risk children and noted significantly higher FE_{NO} levels among children with atopy or physician-diagnosed asthma compared with those without. However, FE_{NO} levels did not differentiate between wheezing phenotypes because children who never wheezed, those with early transient wheeze (at least 1 wheezing episode in the first 3 years of life), those with late-onset wheeze (at least 1 wheezing episode in the fourth year of life), and those who experienced at least 1 wheezing episode in the first 3 years of life and at least 1 episode during the fourth year of life had comparable FE_{NO} levels. Malmberg et al⁷ reported that FE_{NO} levels had a greater combined sensitivity and specificity compared with respiratory function (by means of impulse oscillometry) and bronchodilator responsiveness in identifying preschool children with probable asthma compared with healthy control subjects. In an unselected birth cohort, FE_{NO} levels measured during the first month of life were associated with a significantly increased risk of subsequent respiratory symptoms during the first year of life but only among infants born to mothers with atopy,⁸ suggesting that nitric oxide might have a role in the pathogenesis of respiratory disease early in life and that FE_{NO} levels might help identify children at highest risk for symptoms.

In this issue of the Journal, Moeller et al⁹ report a study designed to examine whether FE_{NO} levels differ between subgroups of preschool children with nonwheezy and wheezing respiratory symptoms. Three groups of children younger than 4 years of age who were undergoing assessment for respiratory symptoms were prospectively enrolled. FE_{NO} levels were measured by using the offline reservoir technique in accordance with American Thoracic Society/European Respiratory Society recommendations. Participants were divided into 3 groups based on their asthma risk according to the Tucson Children's Respiratory Study asthma predictive index³: 190 children with recurrent wheezing and a loose index (< 3 episodes of wheeze per year and 1 major or 2 minor risk factors) for the prediction of asthma at school age, 122 children with recurrent wheezing and a stringent index (≥ 3 episodes of wheeze per year and 1 major or 2 risk factors) for the prediction of asthma at school age, and 80 children with no history of wheeze but who presented with chronic, persistent, or recurrent cough.

The authors report that FE_{NO} levels were significantly higher among children with stringent predictive indices compared with those with loose predictive indices or children with cough. However, FE_{NO} levels did not differ between those with loose predictive indices and those with cough. In a multivariate regression model the only factor associated with FE_{NO} level was the wheezing phenotype (asthma predictive index status), whereas age, sex, passive smoke exposure, allergic sensitization, eosinophilia, and current treatment did not influence FE_{NO} levels. Among children with a stringent predictive index, FE_{NO} levels were higher among participants with allergic sensitization not receiving inhaled

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corticosteroids (ICSs) compared with levels seen in those receiving ICSs, whereas FE_{NO} levels did not differ by ICS use among those without allergic sensitization.

Overall, these findings suggest that eosinophilic inflammation is likely to be present in the airways of children at highest risk for the persistence of asthma symptoms, namely those with positive stringent predictive indices. This would be consistent with recent data confirming the presence of eosinophilic airway inflammation in preschool children with severe recurrent wheeze compared with nonwheezing control subjects.¹⁰

Several caveats must be recognized before consideration of extending these findings into clinical practice. The comparison group in this study was composed of children with cough and without wheeze rather than a group of children without chronic or active respiratory symptoms or a group with manifestations of allergy but without a history of wheeze. No diagnosis was established for this group, and it is possible (and even likely) that a subgroup of these children might have had previously undetected eosinophilic airway inflammation, as suggested in Fig 1 of the article,⁹ which demonstrates a substantial proportion (approximately 15% to 20%) of children in the comparison group with FE_{NO} levels that exceed the median FE_{NO} level for the stringent index group.

Although the FE_{NO} levels among the group of children with stringent predictive indices significantly exceeded those of the group of children with loose predictive indices, there is significant overlap between FE_{NO} levels between these 2 groups, as well as significant overlap between the stringent group and the children without wheeze. These substantial overlaps between categories dampen the utility of this measure in clinical practice. The lack of difference in FE_{NO} levels between the loose index group and the control group is a bit surprising, given the 2.6- to 5.5-fold increased likelihood of active asthma during the school years among children with a loose asthma predictive index,³ suggesting a lesser degree of eosinophilic airway inflammation among those with loose indices relative to those with stringent indices. An alternative explanation for these findings is that the use of ICS therapy was significantly more common in the 2 groups with positive predictive indices than among the comparison group with cough. Given the well-established effect of ICSs on decreasing FE_{NO} levels, the inclusion of children receiving ICSs in this study likely diminished the magnitude of differences in FE_{NO} levels between children with recurrent wheeze and those without wheeze. It is also possible that there exists a differential sensitivity to ICSs between children with stringent and loose indices, with children with loose indices experiencing greater reductions in FE_{NO} levels with ICS therapy.

The clinical application of these findings to subdivide the various wheezing phenotypes in young children would require

the establishment of FE_{NO} cutoff points. Unfortunately, Moeller et al⁹ do not establish cutoff points to identify critical FE_{NO} levels above which persistence of asthma symptoms would be expected to be most likely, nor do they present assessments of sensitivity and specificity for FE_{NO} level as it relates to wheezing phenotype.

The findings of Moeller et al⁹ expand our understanding of the pathophysiologic processes underlying early childhood wheezing syndromes, with increasing evidence that eosinophilic airway inflammation is present in the subset of children with the greatest risk of persistence of asthma symptoms, namely those with stringent predictive indices. It remains to be determined whether the addition of the objective measurement of FE_{NO} to current assessment approaches allows for improved detection of children at highest risk for persistence of asthma-like symptoms. Furthermore, prospective trials including FE_{NO} measurements in young children with recurrent wheeze should be conducted to determine whether it allows for better identification (or prediction) of those children most likely to experience the greatest benefit from therapies such as ICSs.

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