

## EDITORIAL

# Clinical & Experimental Allergy

## SB- $\text{FE}_{\text{NO}}$ : A promising predictor for infants with recurrent wheezing

This editorial discusses the findings of the paper in this issue by M. Elliott et al. [12] pp. 1351–1361.

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Around 30% of newborn infants or toddlers suffer from wheezing. Sixty percent just experience transient wheezing and will resolve spontaneously by school age [1, 2]. Thus, to avoid overtreatment of the transient wheezing children with drugs with potential side effects [3], it is important for clinicians to distinguish those with transient wheezing from those with persistent wheezing. The percentage of peripheral blood eosinophils was found to predict chronic asthma in childhood [4], but this is an invasive test for young children. Since the first report describing the presence of nitric oxide (NO) in exhaled air of animals and humans [5], numerous efforts have been taken to evaluate the value of fraction of nitric oxide in the exhaled air ( $\text{FE}_{\text{NO}}$ ) in the diagnosis and prediction of asthma attracted by its simplicity and noninvasive characteristic [6].  $\text{FE}_{\text{NO}}$  was elevated during asthma, and some studies support the idea that it has a predictive role in the exacerbation of asthma [7, 8], although others have found no association of  $\text{FE}_{\text{NO}}$  with risk of wheezing or asthma [9–11]. There is very little data that have evaluated  $\text{FE}_{\text{NO}}$  as a predictor for future persistence or exacerbations of wheezing in infants and toddlers with recurrent wheezing.

Elliott et al., in this issue of the journal, aimed to determine, in an ongoing longitudinal cohort of infants and toddlers with recurrent wheezing, the predictive values of single-breath  $\text{FE}_{\text{NO}}$  (SB- $\text{FE}_{\text{NO}}$ ), tidal-breathing mixed-expired  $\text{FE}_{\text{NO}}$  (tidal- $\text{FE}_{\text{NO}}$ ), bronchodilator responsiveness (BDR) and the Castro-Rodriguez asthma predictive index [12, 13], for persistence of wheezing, exacerbations and change in lung function over 3 years. This is a follow-up study of their previous

report [14]. In this study, Elliott et al. found that higher enrolment SB- $\text{FE}_{\text{NO}}$  (enrolment mean age 15.6 months) concentrations were significantly associated with persistence of wheezing at age 3 years, acute exacerbations during the 6 months prior to age 3 years, as well as lung function decline. In contrast, enrolment tidal- $\text{FE}_{\text{NO}}$  was not associated with persistence or exacerbations of wheezing. Receiver operating characteristics (ROC) analysis indicated that SB- $\text{FE}_{\text{NO}}$  concentration >30 ppb predict persistence or exacerbations of wheezing, and lung function decline with high specificity and sensitivity. The sensitivity, specificity, positive predictive value and negative predictive value of enrolment SB- $\text{FE}_{\text{NO}}$  were superior to tidal- $\text{FE}_{\text{NO}}$ , BDR and API.

These impressive data by Elliott et al. provide valuable evidence for clinicians to consider SB- $\text{FE}_{\text{NO}}$  as a potential predictor for infants and toddlers with recurrent wheezing and help them identify infants and toddlers who will need medication or treatment to prevent future exacerbations of wheezing.

An important issue is the mechanisms involved in producing nitric oxide in the airways of wheezing or asthmatic children. While  $\text{FE}_{\text{NO}}$  has been widely used as an inflammation marker in patients with wheezing or asthma, it is still poorly understood how nitric oxide is generated and what function it exerts during the inflammation. There are many cell types in the inflammatory airways that can release nitric oxide, such as epithelial cells and macrophages [15]. It remains unknown which cell type derived nitric oxide has more predictive value. In addition, nitric oxide has multiple functions in vivo and can have both protective and toxic effects, perplexing us further [16–18]. Investigating in more detail, the mechanistic aspect of nitric oxide in asthma will help clinicians determine with greater precision the value of this biomarker in the management of childhood wheeze.

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Cite this as: L. Zheng, *Clinical & Experimental Allergy*, 2013 (43) 1307–1308.

**Conflict of interest:** The author declares no conflict of interest.

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