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An Overview of Fractional Exhaled Nitric Oxide and Children with Asthma

Devika R. Rao^a and Wanda Phipatanakul^{b,c,d,e}

^aDivision of Respiratory Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

^bThe Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, USA

^cDivision of Allergy & Immunology

^dBoston Children's Hospital

^eHarvard Medical School, Boston, MA, USA

SUMMARY

Asthma is the most common pediatric chronic disease and is characterized by lung inflammation. Fractional exhaled nitric oxide (FeNO) is thought to reflect the presence of eosinophilic airway inflammation, and is an easy, non-invasive test that has held promise in providing additional objective data. However, not all studies have shown a clinical benefit in the use of FeNO to guide management of asthma in children. This review will describe the results of the most recent studies examining the use of FeNO in the diagnosis and treatment of asthma in infants, pre-school-aged children and in school-aged children. It will aid the clinician in providing a clinical context in which FeNO may be most useful in treating pediatric asthma.

Keywords

Fractional exhaled nitric oxide; pediatric asthma; lung function; infant lung function; sickle cell disease

Overview

There are almost seven million children in the US with asthma, which is the most common chronic pediatric disease, and the incidence is rising [1]. Asthma is characterized by airway inflammation and presence of airway inflammatory mediators, and diagnosis and management is based on clinical history, physical exam and spirometry testing [2]. However, clinical history provided by the child and/or parent can be unreliable and spirometry may not aid in diagnosis or management or reflect airway inflammation [3,4]. Fractional exhaled

CONTACT Wanda Phipatanakul, MD, MS, wanda.phipatanakul@childrens.harvard.edu, Children's Hospital Boston, Division of Allergy and Immunology, Fegan 6, 300 Longwood Ave. Boston, MA 02115, Phone: 617-355-6117; Fax: 617-730-0310.

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nitric oxide (FeNO) has been shown to correlate with levels of eosinophils in the sputum [5] and has been studied as a biomarker tool to help guide clinicians in the management of asthma in children. This paper will review recent evidence in the medical literature that has examined the utility of FeNO in the management of asthma in children.

Nitric oxide (NO) is a signaling molecule produced by respiratory epithelial cells [6], is found in exhaled breath and functions as a vasodilator and bronchodilator in the lungs [7]. NO is synthesized from L-arginine by inducible NO synthase enzymes in response to inflammatory cytokines and is present in the exhaled breath of humans [8]. FeNO has been found to be elevated in children with asthma and is felt to reflect eosinophilic airway inflammation resulting from the type 2 T-helper cell pathway [9,10]. Given that NO is found in exhaled human breath, it was felt that measurement of FeNO could be a noninvasive quantitative measure of airway inflammation, and that FeNO levels could provide clinicians with objective data in the treatment of children with asthma. The potential for FeNO to provide objective data is especially important considering that spirometry and specifically FEV₁ has been shown to be mostly normal in children with asthma of all severities, and in children with symptoms of uncontrolled asthma [3,11–14]. Reduced lung function in school-aged children may be present even in the absence of respiratory symptoms, making the interpretation of spirometry results challenging [15].

Chemiluminescence analyzers were first used in the 1990s to detect NO in exhaled breath, and they were cleared for clinical use by the US FDA in 2003 [16]. FeNO testing is relatively easy to achieve in school-aged children, even in as young as 4 years of age [11], and is therefore practical for clinicians to use to gain objective data about their patients. There are even portable hand-held devices suitable for use in the primary care setting [17]. Furthermore, levels of FeNO are increased in children with asthma compared to children without asthma [10]. In 2011, the American Thoracic Society (ATS) published Clinical Practice Guidelines on the subject of FeNO and recommended that FeNO be used in the diagnosis of eosinophilic airway inflammation [18,19].

Factors that influence FeNO

There are a number of factors that influence FeNO levels, including atopy, height, age, sex, nasal inflammation, respiratory tract infection, consumption of nitrate-containing foods, water, caffeine or alcohol, medication especially inhaled or oral corticosteroids, smoking including passive cigarette smoke exposure, respiratory maneuver, exercise and race [20,21]. Sedentary behavior such as television viewing and video games has also been associated with increased FeNO levels in one study that adjusted for indoor allergen exposure, body mass index and allergic sensitization [22]. In children aged 1–5 years, FeNO has been shown to be unaffected by gender, age, weight or height [23]. One study of infants aged 4–26 months showed that maternal history of asthma was associated with elevated FeNO [24].

Furthermore, the technique used in obtaining FeNO can affect the value, with exhalation flow rate, nasal NO contamination and type of analyzer having an effect on values [18].

There is a well-described association between asthma and obesity [25], and it has been speculated that obesity may lead to increased airway inflammation [26]. However, a recent cross-sectional study by Cibella et al. showed that obesity was not associated with increased FeNO levels [27], a finding that echoed earlier studies [28,29].

Cutoff values of FeNO

The ATS guidelines recommend that a FeNO level of <20 ppb in children indicates that eosinophilic inflammation and responsiveness to corticosteroids is less likely, while a level of >50 ppb likely indicates eosinophilic inflammation is present and good response to corticosteroids [18]. It is recommended that values between 20 and 35 ppb be interpreted within clinical context; in other words, knowing whether the patient is steroid-naïve or knowing the relative change in FeNO values over time. Recent studies appear to support using 20 ppb as a reasonable cutoff value, although these values appear to slightly vary depending on the age of the child and clinical context.

The presence of systemic inflammation may influence FeNO cutoff values. Malinovschi et al. studied the impact of systemic and airway inflammation on asthma morbidity by measuring both FeNO and blood eosinophil levels in adults and children. They found that the risk of current asthma (defined by self-reported wheezing or whistling in the chest in the past year) in subjects with high FeNO (cutoff values of 35 ppb in <12 year olds, 50 ppb in 12 year olds) increased from an adjusted odds ratio of 2.41–5.41 in the presence of high blood eosinophil levels [30]. A similar additive effect was seen on the risk for wheezing, asthma attacks and asthma-related emergency department visits. The authors concluded that systemic inflammation, as measured by blood eosinophils, which are triggered by IL-5 in the TH1 pathway, may have an additive effect on the risk for asthma, wheeze and asthma exacerbations. This study captures those individuals with the highest levels of airway inflammation based on their cutoff values of 35 and 50 ppb; however, this study lends support to considering interpreting FeNO values in terms of serum eosinophilia.

Sivan et al. found that children with FeNO levels of >23 ppb are very likely to have asthma, the false positive rate being <5% [10]. They also found that a FeNO cutoff value of 20 ppb had a sensitivity of 86%, specificity of 89%, positive predictive value of 92% and negative predictive value of 80%. These findings are similar to those described by Peirsman et al., who describe that including FeNO monitoring as a part of asthma management led to fewer asthma exacerbations compared to conventional management. These authors used 20 ppb as their cutoff value when making clinical decisions regarding asthma medications [31]. Sachs-Olsen et al. found in their birth cohort that at age 10 FeNO values of >16.6 ppb were useful in diagnosing current allergic asthma, but not in current nonallergic asthma [32]. This study was based on FeNO values obtained at only one point in time, however. Ghdifian et al. obtained FeNO levels in 80 children aged 6–20 months and found elevated FeNO levels (median of 19.8 ppb) in those with persistent wheezy respiratory symptoms [33]. They found that FeNO levels > 15 ppb had a positive predictive value and negative predictive value for uncontrolled disease of 65% and 90%, respectively (Table 1).

Studies providing FeNO reference values in the infant and toddler ages are generally lacking. However, Van der Heijden et al. recently published reference values of FeNO in healthy children from the Netherlands aged 1–5 years using awake tidal breathing. They found values to be reproducible, and the 95% confidence interval ranged from 2.8 to 11.5 ppb. Gender, age, weight or height did not affect values. Other older studies reporting reference values in this age group are similar or lower, though different techniques of assessing FeNO were used [49–52]. In their study of FeNO in infants with chronic respiratory symptoms, Kotaniemi-Syrjänen et al. used a cutoff value of 27 ppb based on the highest quartile in their cohort [24].

FeNO and diagnosis of asthma

Evidence of bronchial inflammation and eosinophilic inflammation has been found in children prior to the diagnosis of asthma, which may make FeNO monitoring useful early in life to distinguish between children who are more at risk of developing asthma [53]. One study of 52 children aged 5–36 months demonstrated significantly higher FeNO levels in children with a positive asthma predictive index (API) compared to those with a negative API, although the median levels in both groups were low at 12.5 and 5.6 ppb, respectively [34]. FeNO levels have been described to be higher in allergic or atopic asthma compared to nonallergic asthma [45], but are also elevated in children who have allergic sensitization as demonstrated by positive skin-prick testing or aeroallergen-specific IgE [32,35,43]. FeNO levels have been shown to be higher in children with allergic sensitization or atopy and no asthma compared to nonallergic asthma [32,35,45], and have been found to be higher in children both with treated and untreated asthma than in healthy nonatopic children [54].

Results from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort, a prospective birth cohort in the Netherlands, suggest that obtaining FeNO levels later in childhood may be more helpful to distinguish between wheezing phenotypes rather than labeling all wheezing as asthma [36]. Van der Valk et al. described the results of 972 children who underwent FeNO testing at age 8 years. FeNO was highest in children with wheezing that started later in life and persisted longer. Among atopic children (with elevated specific IgE), FeNO was higher in those with infrequent wheezing or transient wheezing, suggesting that wheezing phenotype influences the extent of airway inflammation in sensitized children. At age 4, a higher FeNO level was found among children with late-onset and persistent wheeze, but the association between FeNO and wheezing phenotypes was less strong compared to age 8, suggesting a greater utility of FeNO at an older age. Gouvis-Echraghi et al. also found FeNO is useful in distinguishing asthma phenotypes, but among younger children <36 months of age [37]. They found that FeNO levels were highest (17.7 ± 10 ppb) in children with nonatopic moderate–severe asthma whose symptoms were frequently uncontrolled despite treatment with inhaled corticosteroids (ICS). FeNO levels were not as elevated in the other two wheezing phenotypes, the mild episodic viral wheeze phenotype (6.6 ± 4.6 ppb) and the atopic multiple trigger wheeze phenotype (11.5 ± 10.7 ppb).

An older study by Malmberg et al. suggests that FeNO may be superior to impulse oscillometry in diagnosing asthma among preschool-aged children [42]. In this study,

receiver operating curve analysis revealed that FeNO had superior sensitivity and specificity in discriminating between children with probable asthma based on history and healthy controls.

Neonatal history is important to consider when interpreting FeNO results in the context of asthma. A history of neonatal respiratory distress in preterm infants without bronchopulmonary dysplasia (BPD) may lead to lower FeNO levels in children with atopic asthma, as described in a study by Ricciardolo et al. [43]. A similar finding of lower FeNO levels was previously reported in school-aged children with BPD compared to controls [55], while Filippone et al. found that FeNO levels were similar and normal among former preterm (defined as ≥ 32 weeks gestation) adolescents with BPD, former preterm adolescents without BPD and healthy adolescents born at term, a finding that held true even in the presence of atopy [56]. The children in the former study had higher levels of 8-isoprostane, a marker of oxidative stress, leading to speculation that noneosinophilic inflammation, such as neutrophilic inflammation, may be present in formerly premature children and lead to lower FeNO levels in children with asthma and history of BPD. Schmalisch et al. have shown that former very-low-birth-weight infants undergoing infant lung function testing at an average of 49 weeks postmenstrual age have significantly lower FeNO if they had a history of receiving mechanical ventilation for <7 days compared to not having this history or receiving noninvasive mechanical ventilation [48]. Together, these studies imply that there are changes that may occur in the airway in formerly premature infants with and without history of BPD that may lead to a lower than expected FeNO value. It would behoove clinicians then to consider neonatal history when interpreting FeNO values and considering asthma as a diagnosis.

Finally, alternate diagnoses should be considered when interpreting elevated FeNO values. Elevated FeNO has been described in children with eosinophilic bronchitis, a condition that is characterized by the absence of reversible airflow obstruction, and may be one of the many wheezing phenotypes [57]. In a study by Kim et al., children with eosinophilic bronchitis had higher FeNO levels compared to controls (32 vs. 21 ppb), but not quite as high as children with asthma (40 ppb). Obstructive sleep apnea may increase airway inflammation. A cross-sectional study of children without asthma or allergies showed that FeNO levels are higher in children with obstructive sleep apnea compared to normal controls, although the values reported were <20 ppb [58]. Other conditions in which high FeNO has been found include hepatopulmonary syndrome, liver cirrhosis and bronchiolitis obliterans. Low FeNO has been described in primary ciliary dyskinesia and pulmonary hypertension [59].

FeNO and lung function

FeNO levels have been shown to be increased in children with bronchial hyperresponsiveness (BHR) compared to those without BHR in both normal children and children with allergic sensitization [32]. Elevated FeNO was found to be associated with airway responsiveness as measured by methacholine challenge in 136 former full-term infants with an average age of 16 months and history of chronic respiratory symptoms [24].

Furthermore, presence of bronchodilator response on spirometry has been noted in children aged 7 and younger with elevated FeNO and probable asthma [42].

FeNO has been shown to not correlate with FEV₁ [32] or with FEV₁/FVC percent predicted [11]. One study found a significant but weak correlation between FeNO and FEV₁ [60], while Ricciardolo et al. found an FEV₁ of 86% predicted was associated with FeNO levels between 20 and 40 ppb in children with mild–moderate asthma [43].

Lanz et al. found in a cohort of 21 children aged 4–6 years with asthma that treatment with nebulized budesonide for 2 weeks led to lower FeNO along with a corresponding improvement in FEV₁ from an average of 85–96% predicted [44]. During a washout period where budesonide was discontinued, FeNO level increased while FEV₁ did not worsen, suggesting that FeNO may be more immediately sensitive to withdrawal of ICS compared to spirometry.

FeNO has also been studied in its relationship to infant lung function testing. Schmalisch et al. showed that FeNO levels were negatively correlated with tidal breathing parameters [48]. FeNO decreased with increased expiratory flow, indicating that measuring FeNO in sedated infants exhibiting tidal breathing may not be optimal to achieve a plateau in FeNO signal that is necessary to obtain an accurate value.

Influence of atopy on FeNO

Allergic sensitization as demonstrated by positive skin-prick testing or aeroallergen-specific IgE has been shown to be strongly associated or correlated with elevated FeNO levels [32,61]. The highest FeNO levels may be found in those children who are actively exposed to allergen to which they are sensitized, and in one study, were highest in children sensitized and exposed to dust mite [22]. The number of allergic sensitizations rather than one specific allergic sensitization maybe most important in terms of increased FeNO levels [61]. Some studies have shown that FeNO levels are elevated in children with allergic rhinitis or atopy and no asthma [35,46], and some have not [11,32]. Alveolar NO, as will be discussed later, may be less influenced by atopy [35].

FeNO and asthma exacerbations

Older studies have shown that elevated FeNO may predict asthma relapse after cessation of ICS [62,63], and a recent prospective study of 14 adult patients with eosinophilic asthma showed that longitudinal monitoring over a 24-month period of FeNO compared to conventional monitoring led to reduced symptoms and asthma exacerbations [64]. A recent study examining seasonal risk factors for asthma exacerbations in 400 children with moderate-to-severe persistent asthma found that FeNO predicted fall exacerbations (OR 3.63, CI 1.64–8.04) but not other seasons [65]. An interesting proof-of-concept study examined the utility of daily FeNO measurements in predicting asthma exacerbations over a 30-week period in 77 children with asthma. Although the study ended up including only 27 patients with a total of 37 ‘moderate’ and ‘severe’ exacerbations, the results showed a significant increase in FeNO 10 days before moderate exacerbations [39]. Individual FeNO levels were not helpful in predicting exacerbations; at least four or five data points were

needed (OR 1.92 CI 1.08–3.41; OR 1.79 CI 1.00–3.20, respectively). This study included patients on ICS, which was not accounted for in the final analysis, and therefore, any effect of FeNO on its predictability may have been underestimated.

In a study using fractal and cross-correlation analysis of FeNO-level fluctuations over a period of 30 weeks in 41 children with asthma, Stern et al. found that FeNO levels were strongly associated with symptoms scores on the same day as opposed to FeNO levels lagging behind symptom scores [47]. This relationship was strongest in children who experienced moderate or severe exacerbations, suggesting that when FeNO values and asthma symptoms increase together, this may be reflective of a higher risk of asthma exacerbation. A similar relationship between FeNO levels and symptoms as patient dependent was suggested in adults by Haldar et al. in a phenotype-cluster analysis [66], while another cross-sectional study by Sardón-Prado et al. found that FeNO and symptoms was significantly correlated, but this relationship was weak [60]. Children with more severe asthma may benefit most from FeNO-level monitoring based on these two studies alone.

Further evidence that FeNO levels increase with asthma exacerbations is shown by Karlin et al., who have shown FeNO levels decreased by 23.8% after resolution of an asthma exacerbation [67]. This study also showed that African-American children with asthma exacerbations had higher FeNO levels than compared with Caucasian children (median FeNO of 45 vs. 32 ppb).

A recent meta-analysis of using FeNO as part of asthma management included six studies that compared using FeNO versus conventional methods of asthma management (symptoms, spirometry) [40]. The study included 506 children who were monitored with FeNO and 511 children who were monitored with conventional methods. There was no difference in FeNO values between the two groups, nor any difference in steroid use or FEV₁; however, the FeNO group experienced fewer exacerbations.

FeNO and medication management

The ATS guidelines suggest using a reduction in FeNO of 20% as significantly indicative of a response to anti-inflammatory therapy [18]. A double-blind, randomized, placebo-controlled study of 26 children with mild persistent asthma showed that FeNO was reduced by >60% with sole use of leukotriene receptor antagonist (LRTA) for 4 weeks, after exclusion of children with seasonal atopy and outdoor pollen exposure [68]. It is known that FeNO levels reduce in children and adults with asthma who take ICS [55,69] and that elevated FeNO may reflect increased corticosteroid responsiveness [70]. FeNO levels have been shown to be higher in children with probable but untreated asthma compared to asthmatic children treated with ICS [42]. It has also been described that FeNO levels can be highly variable ranging from low levels to high levels even within one child on stable doses of ICS [47]. Further, FeNO levels may be difficult to clinically predict based on traditional methods of assessing asthma control and may lead a clinician to reconsider dosage adjustment [71].

However, this dosage adjustment may not necessarily be relevant. Earlier studies have examined the possibility of using FeNO measurements in children to guide titration of ICS and the results were not favorable, showing no decrease in emergency department visits when FeNO was used to guide management [72,73]. Jartti et al., in their meta-analysis of four studies comparing asthma management in children using FeNO and conventional methods versus sole use of conventional methods, showed that FeNO monitoring did not result in improved FEV₁ or a reduction of asthma exacerbations [20]. This was despite an overall increase in ICS dose in the four studies by 100 µg, showing that titration of ICS using repeated FeNO measurements may not lead to any clinical benefit. These results are similar to Petsky et al.'s previous meta-analysis of six studies done in both adults and children [74]. Lu et al.'s recent meta-analysis of pediatric trials comparing use of FeNO with use of conventional methods to manage asthma (and included the studies of Jartti et al.) showed that use of FeNO in asthma management did lead to a mildly lower frequency of >1 asthma exacerbations, although no difference was seen in FeNO, lung function or steroid use between the two groups [40].

The most compelling evidence for using FeNO to manage childhood asthma comes from Peirsman et al., who studied asthma management with ICS and LRTA medications in children aged 5–14 years with mild-to-severe asthma and allergic sensitization over a 52-week period [31]. The children were divided into two groups, one in which FeNO was used to determine asthma management using a cutoff value of 20 ppb, and the other in which clinical symptoms, rescue medication use and FEV₁ were used to determine make ICS dosage changes. The authors found that children in the FeNO group experienced less asthma exacerbations over 1 year (18 total exacerbations in FeNO group vs. 35 total exacerbations in clinical group). It was also found that not using FeNO measurements to make asthma management decisions was strongly associated with an increased risk for experiencing 1 exacerbation, even after adjusting for concurrent rhinitis, ICS dose and LRTA use (OR 6.19, 95% CI 2.03–18.85). Cumulative daily ICS dose overall significantly increased from visit 1 to visit 5 in the FeNO group. There was, however, no difference in symptom-free days between the two groups, which was the primary outcome of this trial. Interestingly, FeNO levels did not differ between the two groups and did not change by the end of the study period. This study may have reflected favorably upon FeNO monitoring in part because the definition of an asthma exacerbation was not restricted to exacerbations treated with steroids but also included milder exacerbations. The algorithm used to titrate or step down ICS dosing was also more aggressive than what is recommended by ATS guidelines; if the FeNO level was >20, ICS was increased by 100 µg regardless of symptoms, while the ATS guidelines recommend to consider presence of symptoms [18].

A smaller study of 64 children aged 8–13 years admitted for asthma exacerbations to a pediatric ward in Italy also showed FeNO was useful in management of childhood asthma [41]. These children were randomly assigned to either a FeNO group or 'GINA group', where therapy decisions were based on symptoms, SABA use, lung function or all of these in addition to FeNO measurements. Children were assessed at baseline, and at 6 and 12 months, and the authors found a significant reduction in asthma severity scores and reduction in asthma exacerbation frequency by the end of the study period in the FeNO

group, but not the GINA group. Interestingly, in contrast to the study by Peirsman et al., there was no significant change in use of asthma medications in the FeNO group.

Utility of alveolar NO

Mathematical models have been developed to distinguish the production of NO by the bronchial airways (J_{NO}) from the alveoli (C_{alv}) by measurement of NO at multiple flow rates of 50, 100 and 200 ml/s [75,76]. This technique can be successfully performed by children, although younger children may have trouble completing the test at all flows [35,54]. C_{alv} may not be affected by ICS as much as FeNO, and has been shown to be elevated both in adults and children with asthma treated with ICS [35,77], although a newer study by Sardon et al. showed that there was no difference [54]. Paraskakis et al. showed in their cohort of children, a number of whom had severe asthma, that C_{alv} was elevated in children with asthma, but not in nonasthmatic atopic children [35], suggesting that alveolar NO may be less influenced by atopy compared to conventional FeNO. However, Linn et al. showed that there was significant disagreement in C_{alv} when using different mathematical models other than the one suggested by Tsoukias et al. to determine C_{alv} in children [21]. Puckett et al. found that C_{alv} did not correlate with J_{NO} , and that the subjects, who were predominantly Hispanic and had mostly mild asthma, with higher C_{alv} had worse asthma control and morbidity [78]. These findings were replicated by Corcuera-Elosegui et al. [79]. Overall, a number of studies have found alveolar NO levels to be associated with increased asthma morbidity and poor asthma control in children, although the calculation of this value may be dependent on which mathematical model is used. Given that the above studies were highly variable in terms of ethnicity and degree of asthma severity of the respective cohorts, the degree to which C_{alv} is valuable may be dependent upon these factors.

FeNO in preschool children

Respiratory symptoms including coughing and wheezing are common in the preschool aged child, and the differential is broad [80]. It is difficult to distinguish which of these children are at risk of developing asthma and ICS may not be helpful for all young children who wheeze. Furthermore, respiratory symptoms are non-specific and it can be difficult to predict whether wheezing in the first three years of life will persist into later childhood [15]. FeNO may offer easy-to-obtain additional objective data a clinician may use to determine which children with respiratory symptoms have a high risk of developing asthma.

Moeller et al. showed that FeNO was elevated among preschool-aged children with wheezing and high API compared to children with no wheezing and children with wheezing and low API [81]. Singer et al. found in their prospective study that elevated FeNO in infancy and in the preschool-aged child with a history of recurrent coughing or wheezing was associated with an increased risk of asthma in the school-aged child [38]. The authors also described that the risk increased per each 5 ppb increase in FeNO in the preschool-aged child, and that substituting an elevated FeNO (>10 ppb) for blood eosinophilia as part of the API performed comparably to the traditional API. Using a cutoff of FeNO 10 ppb as abnormal, however, may be too low of a value and has been determined by the ATS to be normal [18], although this has not been specifically determined in the preschool-aged child.

Caudri et al. studied 848 children at age 4 in the PIAMA birth cohort and followed them with annual questionnaires at age 5–8 years [82]. They found that elevated FeNO level at age 4 was associated with increased wheezing and steroid use between age 5 and 8, and increased risk of doctor diagnosed asthma at age 7. They also reported that FeNO, which did correlate with specific IgE levels, was predictive of later asthma symptoms independent of IgE.

Studies of FeNO in infancy

It is a challenge for clinicians to distinguish infants with transient, mostly viral-induced wheezing from those with wheezing that will persist into childhood and later years, and FeNO has been studied as a biomarker to help distinguish between these early wheezing phenotypes and to help predict which infants will develop asthma. FeNO levels have been successfully obtained in multiple studies of infants using the raised-volume rapid thoracic compression method. In one cohort of infants with eczema whose FeNO levels were measured during infancy (mean age 10 months) and followed until age 5, each ppb increase of FeNO during infancy was found to be associated with asthma at age 5 (OR 1.13, 95% CI 1.01–1.26). In this study, high FeNO during infancy was also associated with greater airway reactivity as measured by methacholine challenge at age 5. This study suggests that even subtle differences in airway inflammation that may not be associated with typical asthma symptoms are present very early in life.

One study utilizing the Generation R Study Birth Cohort found that elevated FeNO in infants was associated with an increased risk of wheezing in the second year of life [83]. However, inclusion of FeNO at 6 months in a composite index that included a history of wheezing in the first six months of life and positive maternal atopic disease did not have a better predictive value compared to a clinical index excluding FeNO.

Debley et al. studied children aged 6–24 months with a history of ≥ 3 wheezing episodes and found FeNO to be higher in those who had subsequent wheezing episodes treated with steroids compared to those who did not (39.3 vs. 22 ppb, $p < 0.01$) [84]. They also found that those children with higher FeNO at the initial visit had a greater decline in lung function at the 6-month follow-up visit. This study provides compelling evidence that FeNO has at least short-term predictive value; a 6-month follow-up may not be reflective of wheezing episodes in subsequent years.

Malberg et al. reported the results of their small but interesting study of 36 infants (3–25 months old) with a history of recurrent respiratory symptoms necessitating bronchoscopy for further clinical evaluation [85]. Eosinophils on endobronchial biopsy was an infrequent finding; however, FeNO levels were significantly lower in those infants with neutrophil predominance on biopsy. FeNO levels were higher in a subgroup of atopic infants with eosinophils detected on endobronchial biopsy (26.7 ppb) compared to atopic infants without eosinophils (14.7 ppb, $p = 0.08$). Although a small sample size, this study suggests that neutrophilic inflammation may be the underlying pathophysiological mechanism for recurrent respiratory disease in many infants.

FeNO levels have also been studied in infants recently discharged from the neonatal intensive care unit. Schmalisch et al. suggest that FeNO as clinical monitoring tool in these infants may not be helpful, given that they appear to be significantly influenced by expiratory breathing patterns and invasive ventilation [48].

Exhaled NO and pediatric sickle cell disease

There are many pulmonary manifestations of sickle cell disease (SCD), including asthma, acute chest syndrome, airway hyperresponsiveness, pulmonary hypertension and obstructive sleep apnea. Obstructive lung disease in children with SCD has been described, and it has been hypothesized that since NO is a vasodilator as well as bronchodilator hemolysis in SCD leads to a relative NO-deficient state and thereby airways obstruction [86]. An interesting study compared FeNO levels obtained at multiple exhalation flow rates in 16 children with SCD to 10 children with primary ciliary dyskinesia (also associated with low FeNO levels) and 22 healthy controls [87]. Children with SCD and PCD both exhibited airflow obstruction; however, bronchial NO flux ($\dot{V}_{awNO}$) was significantly increased in SCD compared to the other groups. Alveolar concentrations as well as FeNO at standard exhalation flow rates (50 ml/s) were similar among the three groups. Of note, asthma and atopic phenotypes were excluded from this study, and the authors hypothesize that either subclinical airway inflammation or overall NO dysregulation contributed to their findings. The findings of Radhakrishnan et al. contrast earlier findings by Sullivan et al., who described reduced FeNO in children with SCD, especially in those with a history of acute chest syndrome [88], and low FeNO has been described in adults with SCD [89]. Low FeNO has also been described in subjects with SCD and pulmonary hypertension [90]. Overall, there is a lack of studies describing FeNO in children with SCD. More studies would help to elucidate whether or not SCD is associated with a state of high airway inflammation and NO dysregulation.

Expert commentary

Although the ATS has made specific recommendations regarding the use of FeNO in the diagnosis and management of asthma, many studies show contradictory results in terms of its utility. The most likely reason for these apparent contradictions may have to do with the cohorts themselves, which are characterized by different ages, types of wheezing and various degrees of atopy. What is clear is that FeNO should be interpreted in each individual clinical context.

The most recent body of literature seems to indicate that FeNO may be more useful for certain age groups and wheezing phenotypes. In infant and pre-school-aged children, who are known to have more viral-associated wheezing, FeNO may help to distinguish a phenotype of wheezing that is uncontrolled with ICS. In older children, a high FeNO is more likely to characterize a late-onset persistent wheezing phenotype. A history of BPD may reduce FeNO to a value that is lower than expected, and therefore inquiry into neonatal history may be helpful. In terms of lung function, high FeNO appears to be associated with airway hyperresponsiveness and does not correlate well with FEV₁. FeNO may be more sensitive in predicting asthma exacerbations compared to FEV₁; however, FeNO seems to

correlate poorly with lung function overall. FeNO levels have been shown to increase with asthma exacerbations, but there are not enough studies that have used analysis of daily values to support this. FeNO may be most useful in predicting exacerbations for certain asthma phenotypes and for certain seasons; however, more well-designed studies are needed to further elucidate the predictive value of FeNO. Most studies do not support the use of FeNO to adjust asthma medications, but again, this may be relevant only in certain asthma phenotypes. The utility of FeNO in infants is unclear as normative values have not been established. FeNO may be helpful to predict subsequent episodes of wheezing in infancy, but its use to predict persistent wheezing into childhood is still uncertain. Finally, distinguishing between alveolar versus bronchial FeNO, although not yet commonly done in clinical practice, may be more helpful than standard techniques in the management of asthma and may be more helpful in patients with SCD.

Five-year view

Asthma is a disorder of chronic inflammation in the lungs, and this term is likely an umbrella term for many different phenotypes that behave differently in terms of response to medications and long-term sequelae. These phenotypes are slowly being better studied and described, and will continue to be explored. The role of FeNO within the context of phenotype is yet to be determined, but it appears promising that FeNO will likely be ascribed as being most useful in terms of one or more phenotypes of asthma.

Most experts agree that FeNO provides information regarding airway inflammation, but this information is likely transitory, is very sensitive to ICS, can vary extensively even day to day and is subject to many influences such as diet. Future studies will be most useful if more frequent FeNO data points are obtained over a longer period of time rather than use of cross-sectional data.

Future studies will need to determine the clinical context in which FeNO will be the most useful to diagnose and manage childhood asthma, and will need to continue to address the confounding nature of atopy in order to make FeNO most relevant to the clinician.

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Key issues

- Fractional exhaled nitric oxide (FeNO) is a noninvasive marker of eosinophilic airway inflammation that is influenced by many factors, especially atopy.
- FeNO can be successfully obtained in preschool children.
- FeNO can be also successfully obtained in infants and may be lower than expected in infants with bronchopulmonary dysplasia.
- FeNO does not appear to be well correlated with lung function, but is likely more sensitive to withdrawal of steroids compared to FEV₁.
- FeNO levels are higher in children with asthma and airway hyperresponsiveness.
- FeNO likely reflects a certain phenotype of asthma and may be more elevated in children with later-onset, persistent wheezing.
- FeNO is likely not useful in terms of asthma medication management when compared to conventional methods, but this is largely based on small pediatric trials.
- Alveolar nitric oxide, obtained via a different technique compared to standard FeNO, may be less confounded by atopy.
- FeNO has long thought to be decreased in sickle cell disease, but alveolar nitric oxide may in fact be increased in sickle cell disease, reflecting an overall inflammatory state of this disease that is independent of having a diagnosis of asthma.

Table 1

Summary of recent studies on the use of FeNO in clinical management of pediatric asthma.

FeNO may be useful	FeNO may not be useful
<p>Diagnosis of asthma</p> <ul style="list-style-type: none"> Risk of current asthma was high in setting of high FeNO (>35 ppb) and blood eosinophilia [30] FeNO level >23 ppb was associated with false positive rate for asthma of <5% [10] Infants and toddlers with persistent wheezing had high FeNO [33] High FeNO associated with positive asthma predictive index [34] FeNO was higher in children with treated and untreated asthma compared to healthy nonatopic children [35] Higher FeNO in older children with persistent wheezing [36] Higher FeNO in infants with nonatopic, poorly controlled asthma [37] Alveolar NO may be less influenced by atopy [35] Asthma risk increased per each 5 ppb NO increase in preschool-aged children [38] <p>Prediction and prevention of asthma exacerbations</p> <ul style="list-style-type: none"> FeNO monitoring led to fewer asthma exacerbations (20 ppb cutoff) [31] FeNO may predict seasonal exacerbations in the fall [39] FeNO increased 10 days before moderate exacerbations [39] FeNO monitoring may lead to fewer exacerbations [31,40,41] <p>Lung function</p> <ul style="list-style-type: none"> High FeNO associated with airway hyperresponsiveness [32] and bronchodilator response [42] FeNO between 20 and 40 ppb associated with FEV₁ of <86% [43] <p>Medications</p> <ul style="list-style-type: none"> FeNO may be more sensitive to ICS withdrawal [44] 	<p>Diagnosis of asthma</p> <ul style="list-style-type: none"> FeNO levels are high in atopic children without asthma [32,35,45,46] FeNO levels are lower in children with history of neonatal respiratory distress [43] FeNO levels can be highly variable even within one child [37] <p>Prediction and prevention of asthma exacerbations</p> <ul style="list-style-type: none"> FeNO and symptoms increase together before moderate and severe exacerbations [47] FeNO monitoring did not lead to less steroid use [40] FeNO monitoring did not lead to reduced exacerbations despite increase in IS [20] FeNO monitoring did not lead to less symptom-free days [31] <p>Lung function</p> <ul style="list-style-type: none"> FeNO does not correlate with FEV₁ or FEV₁/FVC [11] FeN decreased with increased expiratory flow in infants [48] <p>Medications</p> <ul style="list-style-type: none"> FeNO is sensitive to ICS use [42]

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids.