

Inflammometry in pediatric asthma: A review of fractional exhaled nitric oxide in clinical practice

Todd A. Mahr, M.D.,¹ Jonathan Malka, M.D.,² and Joseph D. Spahn, M.D.³

ABSTRACT

The burden of pediatric asthma remains high with one-third of patients being under- or overtreated because of the unique challenges in the assessment and management of childhood asthma. Until recently, there has been no point of care tool for assessing the underlying airway inflammation (i.e., inflammometry) in asthma. Recently, fractional exhaled nitric oxide (FeNO) has emerged as an important biomarker for the assessment and management of asthma. Recent evidence indicates that FeNO identifies T-helper cell type 2 (Th2)-mediated airway inflammation with a high positive and negative predictive value for identifying corticosteroid responsive airway inflammation. This article examines the evidence for FeNO as a predictor of Th2-mediated inhaled corticosteroid (ICS) responsive airway inflammation and reviews recent studies evaluating the role of FeNO, whether helpful or not, in the assessment and management of pediatric asthma. FeNO is a reliable adjunct to traditional tests in the assessment of suspected asthma. Importantly, it is useful for identifying and for excluding ICS-responsive airway inflammation. Although individual study results have varied, collectively, asthma managed using FeNO is associated with lower exacerbation rates compared with clinical algorithms alone. Finally, FeNO may be useful in identifying patients at risk for future impairment or loss of asthma control during reduction/cessation of ICS treatment. FeNO testing has an important role in the assessment of pediatric patients with suspected asthma and in the management of pediatric patients with established asthma. Additional studies will continue to define the exact role of FeNO testing in pediatric asthma.

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Asthma morbidity remains high in the United States.^{1–6} The reasons for the persistently high levels of asthma morbidity are multifactorial and include, among others, poor adherence to prescribed medications, differences between specialist versus primary care management, failure of health care providers to follow asthma guidelines or provide asthma action plans, and regional differences in access to health care.^{7,8} In addition, pediatric asthma has four distinct features that make diagnosis and treatment of asthma in this population particularly challenging: (1) symptom reporting often occurs *via* a parent/guardian and not *via* the patient; (2) symptoms are often minimized or denied to avoid a chronic disease diagnosis; (3) lung function is frequently normal (or unobtainable); and (4) inhaled corticosteroids (ICS) are underused because of concerns about long-term side effects.^{9–11}

It is also noteworthy that routinely available tests for the evaluation of asthma such as the Childhood Asthma Control Test (C-ACT) and spirometry are not able to provide information on the status of underlying airway inflammation, the central pathophysiological feature of asthma. Without an objective way to assess airway inflammation, decisions on which medications to provide to individual patients are often subjective. Recently, however, point of care evaluation of the status of airway inflammation *via* assessment of fractional exhaled nitric oxide (FeNO) has become available. Although no asthma evaluation tool is perfect, assessment of airway inflammation using FeNO does bridge an important gap in asthma assessment and management.

ASTHMA PATHOPHYSIOLOGY AND THE ROLE OF NO

Asthma is a heterogeneous, chronic disease characterized by airway inflammation and airway hyperresponsiveness.^{12,13} In allergic asthma, which is the underlying cause of asthma for up to 80% of children,^{14–16} airway inflammation results from the activation of mast cells and antigen-specific T-helper cells type 2 (Th2) resulting in the production of cytokines including interleukin (IL)-4, IL-5, and IL-13 (Fig. 1). In turn, IL-4 and IL-13 cause epithelial inducible NO synthase expression to be up-regulated *via* STAT-6, a process which is corticosteroid sensitive (Fig. 2).¹⁷ Thus, exhaled NO directly signals Th2-mediated, proinflamma-

From the ¹Gundersen Lutheran Health System, La Crosse, Wisconsin, ²Pediatric Associates, Aventura, Florida, and ³National Jewish Health, Denver, Colorado
J Malka is on the Speaker's Bureau for Aerocrine. J Spahn is on the Speaker's Bureau for Aerocrine and GlaxoSmithKline. T Mahr is on the Speaker's Bureau for Aerocrine, GlaxoSmithKline, Genentech, ISTA Pharmaceuticals, Merck, Mylan, and TEVA
Address correspondence and reprint requests to Todd A. Mahr, M.D., Pediatric Allergy/Immunology, Gundersen Lutheran Health System, 1900 South Avenue, C02-007, La Crosse, WI 54601

E-mail address: tamahr@gundluth.org

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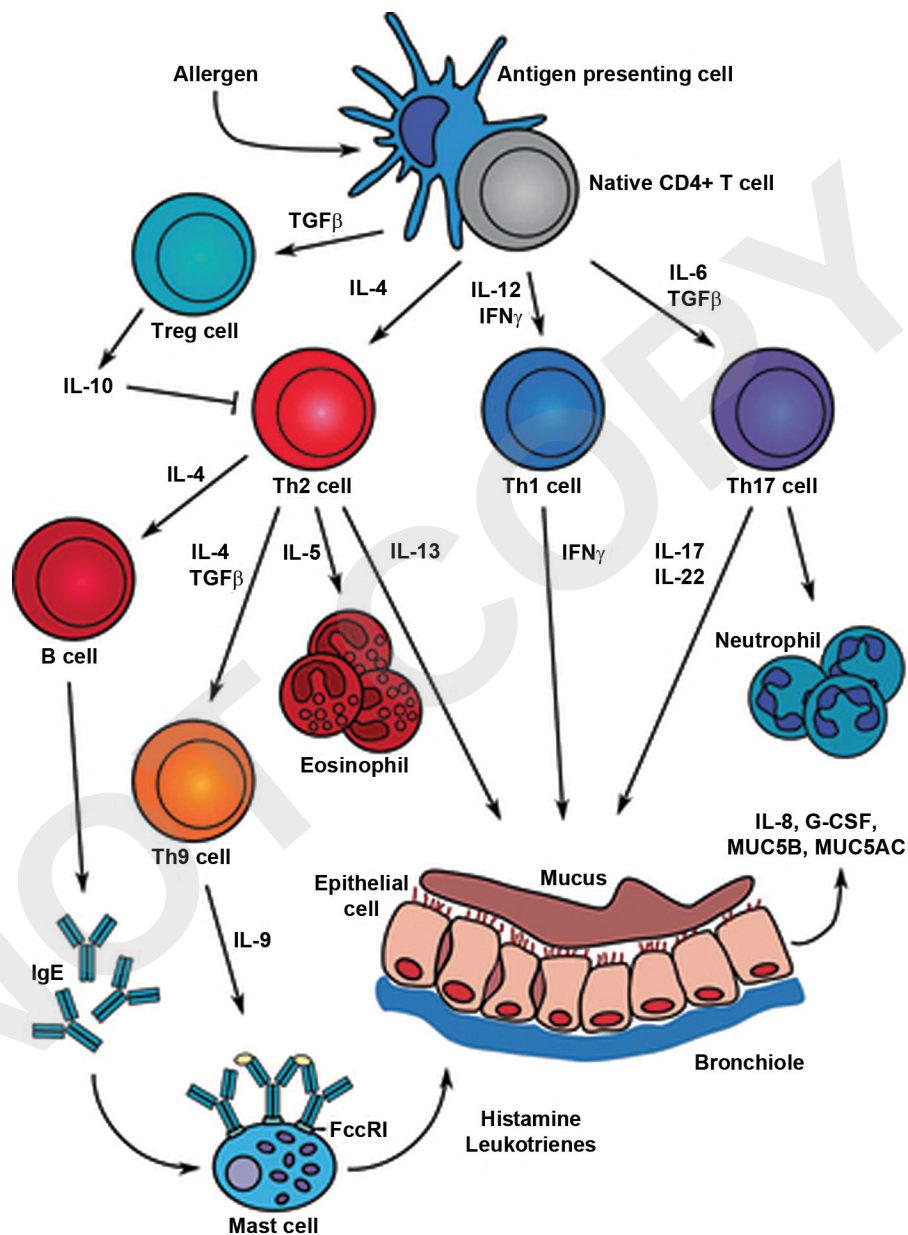


Figure 1. T-helper cell subsets in asthma. (Adapted from Durrant et al., *Emerging roles of T helper subsets in the pathogenesis of asthma*, *Immunol Investig* 39:526–549, 2010.)

tory cytokine mechanisms of central importance in allergic airway inflammation.

FeNO is a marker of Th2-mediated airway inflammation, which is corticosteroid responsive. Although FeNO is also reduced in a dose-dependent manner after treatment with an ICS, it is also recognized that the type, extent, and severity of inflammation is not uniform and varies among patients with asthma.^{18–28} In this regard, six different asthma endotypes have been identified and can be differentiated by various factors including clinical characteristics, underlying airway inflammation cell type, and response to ICS treatment.²⁹ One common asthma endotype is characterized by Th2-mediated airway inflammation, eosinophilia, elevated FeNO, and responsiveness to ICS. By contrast, there is also an asthma endotype that, albeit

less common, is characterized by airway neutrophilia and unresponsiveness to ICS.³⁰ Importantly, unlike traditional parameters such as symptoms and lung function, biomarkers such as FeNO have the ability to help distinguish between these endotypes.

GUIDELINES ON THE USE OF FeNO IN CHILDREN WITH ASTHMA

The American Thoracic Society (ATS) published a clinical practice guideline in 2011 on the “Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications: An official ATS Clinical Practice Guideline.”¹⁸ These guidelines, which have also been endorsed and recognized by the American Academy and American College of Allergy, Asthma, and Immunol-

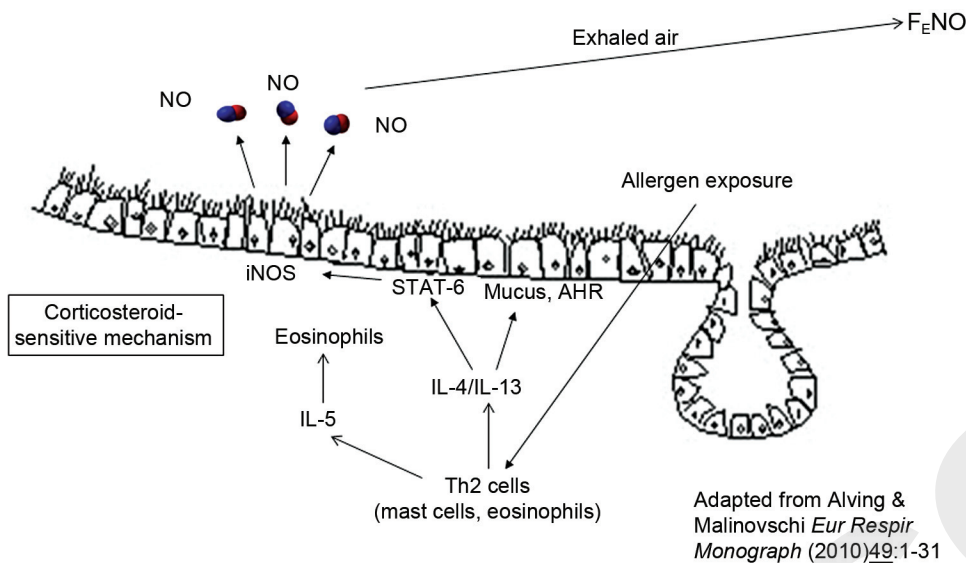


Figure 2. Airway nitric oxide (NO) formation in asthma. (Reproduced with permission of the European Respiratory Society, *European Respiratory Society Monograph* 2010, *Eur Respir Mon* 49 (Exhaled Biomarkers) 1–31; DOI:10.1183/1025448x.00028509.)

Table 1 ATS recommendations and evidence quality

ATS Recommendation	Recommendation Level	Evidence Quality
Use of FeNO in the diagnosis of eosinophilic airway inflammation	Strong	Moderate
Use of FeNO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly caused by airway inflammation	Strong	Low
Use of FeNO to support the diagnosis of asthma in situations where objective evidence is needed	Weak	Moderate
Use of cut points rather than reference values when interpreting FeNO levels	Weak	Low
Accounting for age as a factor affecting FeNO in children <12 yr of age	Strong	High
A FeNO <20 ppb in children (<25 ppb in adults) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely	Strong	Moderate
A FeNO >35 ppb in children (>50 ppb in adults) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely	Strong	Moderate
A FeNO value between 20 and 35 ppb in children (25–50 ppb in adults) should be interpreted cautiously and with reference to the clinical context	Strong	Low
Accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FeNO	Strong	Moderate
Use of FeNO in monitoring airway inflammation in patients with asthma	Strong	Low
An increase of >20% in FeNO for values >50 ppb or >10 ppb for FeNO values <50 ppb is considered significant	Weak	Low
A decrease of ≥20% for FeNO values >50 ppb or >10 ppb for FeNO values <50 ppb indicates a significant response to anti-inflammatory therapy	Weak	Low

Source: Adapted from Ref. 18.

ATS = American Thoracic Society; FeNO = fractional exhaled nitric oxide.

ogy, are evidence based and designed to guide the use and interpretation of exhaled NO measurements in clinical practice.³¹ A summary of the key guideline recommendations is provided in Table 1. In interpreting these recommendations, it is important to note that

the ATS evidence supporting each recommendation was graded according to published ATS GRADE standards as high, moderate, low, or very low.³²

Although the emergence of new evidence will change the evidence level for some of these recommen-

dations, the evidence level is moderate for the following strong recommendations, which are very relevant to the day-to-day management and assessment of asthma in the pediatric population: (1) detecting eosinophilic airway inflammation, (2) determining the likelihood of corticosteroid responsiveness, (3) monitoring airway inflammation to determine the potential need for corticosteroids, and (4) identifying nonadherence to corticosteroid therapy.

FeNO AND ASTHMA ASSESSMENT IN CHILDREN

Tests that are commonly used in the assessment of children with suspected asthma do not, with the exception of sputum eosinophils, assess airway inflammation, which is the central pathophysiological feature of asthma. The emphasis of pulmonary function tests is to identify airway obstruction, not airway inflammation. In addition, the cooperation and effort required to correctly perform spirometry makes this test impractical, especially for children <6 years of age. Furthermore, even when an acceptable spirometry reading can be obtained, the results are often normal or supernormal.³³ Consequently, there is a need for adjuncts to spirometry and routine clinical assessment tools assessing suspected asthma in pediatric subjects.

FeNO has been shown to be useful as an adjunct to traditional tests in the assessment of suspected asthma. FeNO levels have been shown to correlate well with sputum eosinophils,^{23,25,34,35} blood eosinophils,³⁶ serum eosinophilic cationic protein,³⁶ and IgE levels.^{36,37} However, FeNO is also useful as an indicator of ICS-responsive airway inflammation and, more importantly, for identifying airway inflammation that will not respond to corticosteroids. These principles are embodied in the 2011 ATS guidelines, which recommended the use of normal ranges and clinical cut points when interpreting FeNO values. Specifically, the ATS guidelines indicate that an FeNO of <20 ppb (<25 ppb in adults) is a strong indicator that ICS responsiveness is unlikely and an FeNO of >35 ppb (>50 ppb in adults) is a strong indicator that ICS responsiveness is likely.

FeNO levels in nonasthmatic children and adults have also recently been evaluated using data from the National Health and Nutrition Examination Survey 2007–2010 data set. The 95th percentile for FeNO was determined to be 36 ppb (age, <12 years) and FeNO levels above these values are indicative of airway inflammation. The authors also found that predictive equations did not adequately explain the variation observed in FeNO in the general population, providing further support for the recommendation of the ATS that clinical cut points rather than predictive equations be used when interpreting FeNO values in children and adults.

The evidence for the high positive and negative predictive value of FeNO for identifying corticosteroid-responsive Th2 airway inflammation continues to increase and has recently been reviewed by Taylor *et al.*³⁸ Specifically, the usefulness of FeNO for identifying corticosteroid-responsive Th2 airway inflammation has been evaluated in subjects with various airway diseases (*e.g.*, asthma, chronic obstructive pulmonary disease, and chronic cough) and varying prior asthma medication histories (*e.g.*, steroid naïve asthma and severe asthma on ICS). These studies show three key points: (1) FeNO is substantially better for predicting ICS responsiveness than conventional measures such as peak flow rates, spirometry, and bronchodilator responsiveness^{39–41}; (2) the negative predictive value of FeNO for predicting ICS nonresponsiveness is very high across the asthma studies (91–95%) at cut points of FeNO that generally range from 20 to 30 ppb; and, (3) the positive predictive value of FeNO for identifying ICS responsiveness is also high, ranging from 79 to 88% when the FeNO cut point is ≥ 47 ppb.

In interpreting FeNO in children with suspected but undiagnosed asthma, it needs to be recognized that individuals with various atopic conditions may have elevated FeNO levels relative to healthy subjects, regardless of respiratory symptoms.²³ However, FeNO is able to help distinguish asthma from other nonasthmatic allergic conditions such as allergic rhinitis (AR), eczema, and atopy.³⁷ Nonetheless, the phenotypic characteristics of childhood asthma is variable and not all children with established asthma have eosinophilic airway inflammation. In a review by Bush *et al.*,⁴² it was noted that there are children with asthma who have predominantly neutrophilic airway inflammation as well as children with paucicellular airway inflammation in whom FeNO levels are not elevated. However, FeNO is able to help identify the most common type of asthma in children (*i.e.*, atopic asthma), often without the need for additional testing such as induced sputum and methacholine challenge. In addition, as noted previously, FeNO is particularly useful for identifying airway inflammation that will not respond to corticosteroids, an outcome that would be expected in children with predominantly neutrophilic airway inflammation or paucicellular airway inflammation.

FeNO and Asthma Assessment in Preschool Children

Assessing asthma in preschool children can be challenging given the subjective nature of symptoms in this age group and the difficulty in performing diagnostic tests including spirometry and FeNO.^{43–45} However, in tertiary centers where access to specialized techniques to measure FeNO are available, the usefulness of FeNO

for predicting the development of asthma, changes in lung function, and risk of future wheezing in preschool children has been evaluated.^{46–50} Moeller *et al.*⁴⁶ evaluated three groups of children: group 1 had chronic persistent or recurrent cough without a history of wheezing, group 2 had less than three episodes of wheezing per year and one major or two minor criteria for asthma, and group 3 had three or more episodes of wheezing per year and at least one major or two minor criteria for asthma. Children in group 3 had significantly higher FeNO levels than children in groups 1 or 2.⁴⁶ Malmberg *et al.*⁴⁷ indicated that FeNO measurements were superior to baseline respiratory lung function and bronchodilator responsiveness in predicting asthma in preschool children. Likewise, Caudri *et al.*⁴⁸ indicated that FeNO measured at age 4 years was predictive of wheezing and asthma at age 8 years. Van der Valk *et al.*⁵⁰ evaluated FeNO in children from 4 to 8 years of age with varying phenotypes based on history and onset of wheezing. They found that FeNO levels at age 8 was associated with specific wheezing phenotypes but only among atopic children. Finally, Debley *et al.*⁴⁹ conducted a longitudinal pilot study in children <2 years of age with a history of recurrent wheezing. FeNO was measured at baseline and the children were followed for 6 months. Increased FeNO levels were shown to be associated with decreases in lung function, increased risk for an exacerbation requiring systemic corticosteroids, and bronchodilator responsiveness.

Although FeNO testing has shown promise as a diagnostic and predictive tool in preschool children, additional studies are needed, to more comprehensively evaluate the role of FeNO, and other diagnostics tests are needed in diagnosing asthma and also in identifying children who are at increased risk for developing asthma later in childhood.

Practical Considerations for Use of FeNO in Assessing Asthma

When interpreting FeNO levels, factors that can confound FeNO levels need to be considered.^{18,33} Factors that may cause elevations in FeNO include viral airway infection and a nitrate-rich diet. AR may be associated with increases in FeNO higher levels. However, FeNO levels in patients with AR and asthma are much higher than in AR alone.³⁷ FeNO levels are reduced by smoking and corticosteroid administration. Finally, FeNO should be measured before spirometry and bronchodilator administration because both may affect FeNO levels, although the affect is small.^{18,51}

There are other practical issues to consider when assessing FeNO in children. First, FeNO increases with age in children, most likely reflecting the increase in airway size as the child grows. An increase from 120 to

180 cm in height was associated with an increase in FeNO from 7 to 14 ppb.⁵²

Second, age impacts the technical feasibility of performing FeNO testing. Single-breath online measurement of FeNO at a flow rate of 50 mL/s is currently the recommended method for measuring FeNO.⁴³ The NIOX MINO (Aerocrine, Morrisville, NC) is cleared by the Food and Drug Administration for patients aged ≥ 7 years in the United States and for patients ≥ 4 years of age outside the United States.^{43,53} In addition, normal values have not been established in preschool-aged children, and children <6 years of age may experience difficulty with FeNO testing.³³ Alternatives for children who can not perform a FeNO measuring using the single-breath online technique include various off-line measurement techniques.^{43,54,55} However, these alternate techniques have not been validated or standardized and thus are not recommended for clinical use.

FeNO AND ASTHMA MANAGEMENT IN CHILDREN

As previously noted, FeNO levels are useful for identifying Th2-mediated airway inflammation that is responsive to corticosteroids.^{18,19,22–27} This is reflected in the ATS guidelines, which recommend using FeNO to monitor airway inflammation and to guide anti-inflammatory treatment in patients with established asthma.¹⁸ To date, the number of studies comparing FeNO-based asthma management algorithms with standard asthma management algorithms in adults and children has been relatively limited. However, a Cochrane systematic review of FeNO-based asthma management was published in 2009.⁵⁶ In addition, Petsky *et al.* published a meta-analysis of studies evaluating FeNO or sputum eosinophils for the management of patients with asthma in 2012.⁵⁷ Based on these analyses, it has been concluded that the use of FeNO in clinical practice can not be recommended for adults or children and that future studies are needed.^{56–58}

The primary outcome of both the Cochrane systematic review and the Petsky meta-analysis was the number of participants who had asthma exacerbations during follow-up. In analyzing these data, it is important to consider how an exacerbation was defined in each of the studies (Table 2). Although asthma exacerbation definitions were not uniform, the criteria set forth by the ATS/European Respiratory Society guidelines for a severe asthma exacerbation was generally met for each of the studies conducted in children. In this meta-analysis, children were defined as subjects with asthma between 6 and 20 years of age.

Figure 3 shows the results for the number of exacerbations from the original Cochrane meta-analysis for both the adult and the pediatric population. The num-

Table 2 Studies comparing FeNO-based asthma management algorithms with standard asthma management algorithms: Definition of exacerbations

Study	Age Range (yr)	Study Duration	Exacerbation Definition
De Jongste <i>et al.</i> ⁶¹	6–18	30 wk	Course of oral corticosteroids, ER visit or hospital admission
Pijnenberg <i>et al.</i> ⁷⁶	7–16	24 wk	Course of oral corticosteroids and/or need for rescue bronchodilators of ≥4 days/wk for at least 2 consecutive wk or mean diurnal PEF variability of >20%
Szeffler <i>et al.</i> ⁶⁰	12–20	46 wk	Composite outcome consisting of hospital admission, unscheduled visits, and a course of oral corticosteroids

ER = emergency room; FeNO = fractional exhaled nitric oxide; PEF = peak expiratory flow.

Figure 3. Forest plot of comparison of two studies: Number of subjects who had one or more exacerbations over the study period. (Adapted from Petsky *et al.*, Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults, *Cochrane Database Syst Rev* 7(4): Cd006340, 2009.)

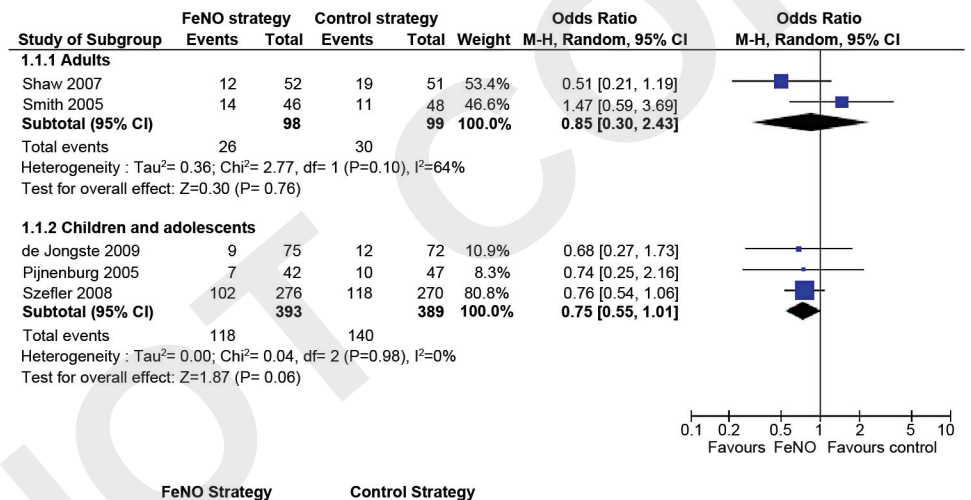
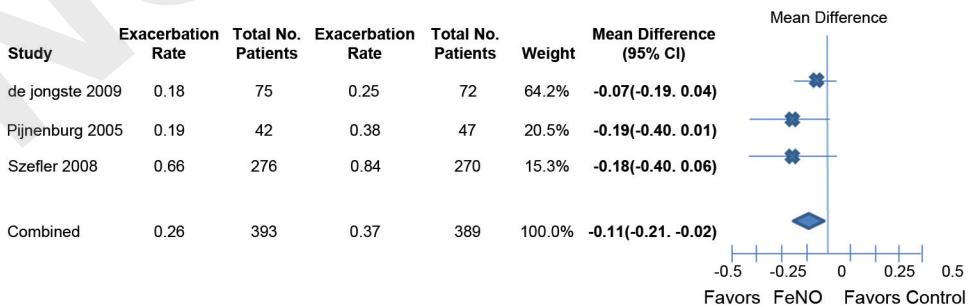


Figure 4. Forest plot comparison of asthma exacerbation rates after fractional exhaled nitric oxide (FeNO)-based versus clinically based asthma management in children.



ber of pediatric subjects with asthma exacerbations was numerically lower for subjects managed using FeNO compared with subjects managed using clinical parameters alone for all of the studies; and the upper limit 95% CI fell just outside the margin of significance (odds ratio [OR] = 0.75 in favor of FeNO; 95% CI, 0.55, 1.01).

The analyses described previously were based on the number of patients with exacerbations; however, this end point is not considered the most appropriate end point for assessing exacerbations because it does not take into account subjects who had multiple exacerbations. In this regard, the time to first asthma exacerbation and/or asthma exacerbation rates are considered by the National Institutes of Health to be the most

appropriate outcomes for assessing asthma exacerbations.⁵⁹ The data from FeNO studies conducted in children in the original Cochrane⁵⁶ systematic review and the Petsky⁵⁷ meta-analysis has thus been updated to include a complete meta-analysis of asthma exacerbation rates (Fig. 4). This analysis shows that the rate of exacerbations is significantly reduced, in favor of the FeNO-based asthma management strategy in children (mean treatment difference, -0.11; 95% CI, -0.21, -0.02), indicating that FeNO-guided asthma management in children is superior to asthma managed using clinical parameters alone with respect to asthma exacerbation rates.

As with all treatments or treatment approaches used in patients with asthma (children and adults), it is

Table 3 Studies comparing FeNO-based asthma management algorithms with standard asthma management algorithms: ICS dose at end of study

Study	ICS Dose At the End of the Study		Treatment Difference (μg)	95% CI
	FeNO Strategy Mean (SD; μg)	Control Strategy Mean (SD; μg)		
de Jongste <i>et al.</i> ⁶¹	475 (504) <i>n</i> = 77	444 (628) <i>n</i> = 74	40	−167, 227
Pijnenberg <i>et al.</i> ⁷⁶	935 (656) <i>n</i> = 39	910 (678) <i>n</i> = 46	25	−259, 309
Szeffler <i>et al.</i> ⁶⁰	1120 (966) <i>n</i> = 276	880 (823) <i>n</i> = 270	240	87, 393

FeNO = exhaled nitric oxide; ICS = inhaled corticosteroid.

important to consider the risk: benefit ratio. For a comparison of FeNO-guided asthma management with asthma managed using clinical parameters alone, the corticosteroid requirements for each management strategy must be assessed. As shown in Table 3, ICS dose at the end of the study for the FeNO and control strategies was similar for two of the three studies. Although ICS dose was higher by $\sim 240 \mu\text{g}$ for the study by Szeffler *et al.*,⁶⁰ this study had design characteristics that predetermined this result. Specifically, subjects were not eligible for randomization until they completed a 3-week run-in period that was designed to eliminate noncompliant patients. At the end of the run-in period, asthma control had improved considerably and was high in both groups. This observation was reflected in FeNO levels that had gone from 31.7 ppb at baseline to 20.5 and 19.7 ppb in the FeNO and control groups, respectively. Thus, although ICS dose over the course of the study fell in both groups, it is not surprising that the ICS requirements were higher in the FeNO group for two main reasons: (1) symptoms, β -agonist use, and lung function were used in the same way to drive the need for changes in treatment in both groups and (2) FeNO levels could be used to increase ICS dose even when asthma was otherwise controlled; however, the ICS dose could not be reduced when FeNO levels were low unless all other aspects of their asthma were also controlled. This is in contrast to other studies in children and adults where requirements for high medication compliance and control were not study entry requirements. In these studies, ICS requirements were either similar for the FeNO and control strategies^{61–63} or were lower in favor of the FeNO strategy.^{40,64}

Although not part of the original meta-analysis, one additional study in children has recently been published. Specifically, Pike *et al.* compared the ability of FeNO-driven or standard asthma management to reduce ICS dose and exacerbation frequency in 90 children 6–17 years of age with moderate-to-severe

asthma.⁶⁵ In this relatively small study (34 completers in the FeNO arm and 43 completers in the standard management arm), no difference was found between the two groups in either ICS dose or exacerbation frequency in this study.

In summary, studies comparing FeNO with usual clinical management of pediatric asthma have generally indicated that exacerbation rates are reduced while ICS requirements are generally neutral. The preponderance of data thus indicates that the risk/benefit ratio is positive for FeNO and that FeNO has an important role in the management of pediatric patients with asthma. Additional studies will continue to define the exact role of FeNO testing in pediatric asthma.

FeNO and ICS Responsiveness and Compliance

FeNO is useful as an indicator of ICS responsive and Th2-mediated airway inflammation, and FeNO has been shown to have greater value for predicting ICS responsiveness in a population of patients presenting with undiagnosed asthma symptoms than conventional measures such as peak flow rates, spirometry, and bronchodilator responsiveness.⁴¹ In this regard, Szeffler *et al.*⁶⁶ conducted an 8-week, two-period, crossover study in 144 patients who were 6–17 years of age with established asthma. Patients received fluticasone propionate at $100 \mu\text{g}$ twice daily or montelukast once daily during the study. This study showed that elevated FeNO levels, as well as other markers of inflammation, were significant predictors of responsiveness to an ICS versus a leukotriene receptor antagonist in children with mild-to-moderate asthma.⁶⁶ This finding was reinforced in a 1-year study performed by Knuffman *et al.*⁶⁷ who sought to identify phenotypic characteristics that could predict differences in treatment response in a double-blind, parallel-group study comparing low-dose fluticasone to montelukast in children with mild-to-moderate asthma. The authors found fluticasone-treated

children to have a significantly greater number of asthma control days than montelukast-treated children. An elevated FeNO level (≥ 25 ppb) predicted response to fluticasone therapy while no study parameter predicted a response to montelukast. Of note, no lung function parameter predicted a treatment response to either agent.⁶⁷ Finally, Berry *et al.*²⁷ have shown that adult patients with eosinophilic asthma (as documented by bronchial biopsy and bronchoalveolar lavage) and high FeNO levels at baseline were responsive to ICS treatment, whereas patients with noneosinophilic asthma and low FeNO levels at baseline were not.

In addition to being an indicator of ICS-responsive airway inflammation, FeNO is useful for assessing adherence with ICS therapy in patients with established asthma. Beck-Ripp and colleagues⁶⁸ evaluated FeNO levels in children in a placebo-controlled study following sequential changes in budesonide. FeNO, but not conventional lung function tests, were able to differentiate between children treated with or without budesonide. In another study conducted in 30 children 7–17 years of age with persistent asthma, a significant correlation between FeNO levels and corticosteroid compliance was shown ($r = -0.76$; $p = 0.001$).⁶⁹ This information is important in clinical practice because ICS compliance rates are known to be low (range, 20–73%) and FeNO can help identify patients whose lack of asthma control is caused by ICS noncompliance and thus help avoid overprescribing of unneeded asthma medications.⁷⁰

Use of FeNO for Predicting Relapse and Identifying “At-Risk” Patients

A number of recent studies have examined the role for FeNO in identifying children who are at risk for experiencing poor asthma control,^{69,71,72} exacerbations,^{73–75} and failing ICS withdrawal.^{76,73} For example, in a cross-sectional study of 304 patients ≥ 12 years of age with established asthma, the likelihood of having seven or more short acting β -agonist canisters dispensed or two or more courses of oral corticosteroids for asthma exacerbations in the follow-up year was 2.26 and 3.26 times more frequent, respectively, for subjects whose FeNO values were $>300\%$ predicted.⁷¹ Additionally, Zacharasiewicz *et al.*⁷³ conducted a study in 40 asthmatic patients 6–7 years of age who were candidates for ICS dose reduction. The patients were seen every 8 weeks and the ICS dose was decreased if clinically indicated. Over the course of the study, 30 patients were able to undergo at least one ICS dose reduction, 12 patients had their ICS completely stopped, and 15 patients developed a loss of asthma control during the study. Multiple logistic regression indicated that an increase in FeNO was a highly sig-

nificant predictor of failed ICS dose reduction (OR = 6.3; 95% CI, 3.75, 10.58). Similarly, in a retrospective evaluation of data from the Childhood Asthma Inflammatory Respiratory Status Monitoring study, Stern *et al.*⁷⁵ evaluated 41 subjects 6–18 years of age with asthma who had adequate daily FeNO data for evaluation. FeNO was measured daily for 30 weeks and ICS doses were adjusted every 3 weeks based on symptoms and FeNO levels. In this proof-of-concept study, the authors concluded that monitoring fluctuations in FeNO levels better identified children at risk for exacerbations than mean FeNO values. Although additional studies in this area are needed, these data suggest that FeNO may be useful in identifying patients at risk for future impairment or loss of asthma control during reduction/cessation of ICS treatment.

It must also be noted that a recent study by Yavuz *et al.*⁷¹ was conducted to evaluate the role of FeNO and C-ACT in identifying children whose asthma was not well controlled. This study, which was conducted in 76 children 6–11 years of age with asthma suggested that C-ACT was better than FeNO in identifying patients with uncontrolled asthma. However, despite the fact that the majority of subjects in the study had mild or intermittent asthma and were well controlled, an FeNO of ≥ 19 ppb was still shown to be a significant indicator of not well-controlled asthma (OR = 2.60; 95% CI, 1.67, 6.29; $p = 0.03$).

CONCLUSIONS AND FUTURE DIRECTION

FeNO testing has emerged as a noninvasive, inexpensive, reliable indicator of corticosteroid-responsive Th2-mediated inflammation for use in the assessment and management of asthma. In addition to its role in assessing and managing asthma in children, FeNO testing is also useful for monitoring adherence to anti-inflammatory medications, identifying patients with high persistent allergen exposure, predicting exacerbation risk, and guiding decreases in or cessation of ICS therapy. Used in conjunction with conventional measures of asthma control, FeNO provides health care providers with valuable information that contributes to a more complete assessment of asthma severity and control in children.

The body of evidence for the use of FeNO in asthma will continue to be investigated and refined in coming years. However, taking into account the accumulated evidence, including the data from new analyses in this article, FeNO has an important role in the assessment of pediatric patients with suspected asthma and in the management of pediatric patients with established asthma. Additional studies will continue to define the exact role of FeNO testing in pediatric asthma.

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