Exhaled Nitric Oxide in Pediatric Asthma

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Exhaled nitric oxide can now be measured in a clinical setting as a noninvasive, reproducible, facile, point-of-service test to measure airway inflammation, a central component of asthma that had not been assessed previously. An excellent surrogate marker of steroid-responsive eosinophilic airway inflammation, it serves to identify steroid-sensitive asthmatic patients and enables clinical monitoring of the response to steroid therapy and titration of the dose. Standardization of methodology and technological advances, such as the recent availability of handheld analyzers, individualized patient cards to store serial test measurements, and the assignment of coding procedural terminology, make this a necessary adjunct to clinical and functional assessment of airway obstruction and hyperresponsiveness in ambulatory pediatric and adult asthma practices.

Introduction

Asthma is a multifaceted syndrome comprising the elements of bronchial hyperreactivity and variable airway obstruction and driven by underlying chronic inflammation with consequent reversible and irreversible changes in the airway. In the past few decades, tremendous strides have been made in our understanding of asthma and the pathophysiologic mediators involved in the inflammatory process. This insight has enabled illuminating phenotypic classifications of asthma based on the type of inflammation (eosinophilic/neutrophilic/paucigranulocytic), assessment of severity (intermittent/persistent to mild/moderate to severe), age at onset (childhood/adult), presence of atopy (allergic/nonallergic), pharmacologic response (corticosteroid responsive/corticosteroid resistant), degree of control (well controlled/poorly controlled), and disease activity status (symptomatic/asymptomatic/remission). Although assessment of bronchial hyperreactivity, along with symptoms and airflow limitation, remain the keystone of asthma diagnosis, the advent of novel biomarkers that provide insight into the nature of inflammation have provided us with the enviable ability to predict clinical response to anti-inflammatory medication. Airway diseases characterized by eosinophilic inflammation are more likely to benefit from corticosteroid therapy, both systemic and topical. The launch of US Food and Drug Administration (FDA)-approved devices to measure exhaled nitric oxide (NO) noninvasively has opened an exciting new portal into improved individualized clinical care of asthma. In contrast to induced sputum, fractional concentration of exhaled NO (F_ENO) measurements are easy to perform in children over the age of 4 years and adults and are reproducible. The advent of newly approved handheld devices enables incorporation into office-based practices. With the standardization of F_ENO measurement techniques, a large body of published literature (> 1500 articles), support for its use in the recent asthma guidelines [1], and increasing use in research and clinical practice, F_ENO has insidiously carved a niche in routine asthma management. This review attempts to complement previous excellent reviews on this topic by objectively and subjectively describing the use of F_ENO in ambulatory pediatric asthma management.

Summary of Biology and Functions of Nitric Oxide

As reviewed earlier [2], NO is a gaseous molecule initially believed to be an atmospheric pollutant and later recognized—in the 1980s—as an endogenous mediator contributing to muscle relaxation. It was heralded as the Molecule of the Year in 1992 and discovered to be a short-lived, endogenously produced gas that acts as a signaling molecule in the body, a Nobel Prize–winning discovery. The landmark observation that endogenous NO can be measured in exhaled breath [3] and subsequent observations that NO levels were high in asthma and decreased after steroid use resulted in intense scrutiny of F_ENO levels in asthma and other inflammatory lung diseases [4].

Endogenous NO is derived from L-arginine by the enzyme NO synthase (NOS), of which at least three distinct isoforms exist. Constitutive NOS isoforms include NOS 1 (neuronal NOS) and NOS 3 (endothelial NOS), named for their discovery in nervous tissue and vascular endothelium, respectively. The third isoform—the inducible, calcium-independent NOS (also called iNOS/*NOS2A*)—is induced by proinflammatory cytokines, endotoxins, and viral infections and is increased in asthma and allergic rhinitis [5].

The functions of NO in the lung include neurotransmission, vasodilatation, bronchial dilatation, and immune enhancement. However, NO's actual role in asthma is unclear. In low concentrations, NO has been shown to have bronchodilatory and antioxidant effects. Paradoxically, at higher concentrations, it is proinflammatory and predisposes to bronchial hyperresponsiveness. Although F_ENO is elevated in many disease states, measurement of these levels is perhaps most clinically useful in allergic airway disease [6].

Online Measurement of F_ENO

Measurement of F_ENO can be performed by online or offline techniques, although current FDA-approved devices favor the online methodology using the single-breath technique [7]. F_ENO levels are flow dependent and inversely proportional to the expiratory flow rate. A high flow rate results in low F_ENO, and vice versa. The flow rate therefore needs to be scrutinized when analyzing and comparing F_ENO levels across studies, particularly those done before guidelines were published in 1999 [7]. Because a large amount of the F_ENO comes from the upper airways, exhalation against positive pressure, causing the velum to close, is also recommended. The patient inhales NO-free gas to total lung capacity and exhales at the recommended 50 mL/sec (regulated through an inline resistance) using a computer graphic interface until an NO plateau of more than 2 seconds can be identified during an exhalation of more than 4 seconds. The maneuver is repeated three times to ensure reproducibility.

Devices to Measure Online F_ENO

The FDA cleared the Aerocrine exhaled NO monitoring system (NIOX; Aerocrine, Solna, Sweden) for clinical applications in patients with asthma in May 2003 [8]. The labeling of this device is currently restricted to the monitoring of response to anti-inflammatory medications, as an adjunct to clinical and laboratory assessments, in children and adults between the ages of 4 and 65 years. A newer model (NIOX FLEX) is also available. Airway NO is measured by its reaction with ozone, which is detected by chemiluminescence. These analyzers are fast-responding, highly sensitive (detection limit ≤ 1 parts per billion [ppb]), and specific for NO gas. However, they are also rather bulky and expensive, must be calibrated on site, and therefore are appropriate for academic centers and specialty clinics [9••]. The FDA labeling restricts the operation of the NIOX device to trained physicians, respiratory therapists, nurses, and laboratory technicians. The NIOX FLEX system is sold in a start package that includes the NIOX FLEX base unit, user interface (keyboard and monitor), mouse, calibration gas, installation, and training. The US price is about $43,000. Operational costs include $134 every 6 months to replace the NO scrubber, $44 (package of 10) for monthly replacement of two fan filters, and $1400 every 9 months for calibration gas. The NIOX system has to be serviced every 18 months ($4400). Each test consumes a disposable mouthpiece filter ($4). A single test costs about $165 (Aerocrine, personal communication).

The NIOX MINO was introduced in Europe in 2005 and recently has been cleared by the FDA for clinical use in adults and children older than 7 years [10]. It has an electrochemical sensor based on the amperometric technique (the production of a current when a potential is applied between two electrodes) inserted into the device. The advantages of the NIOX MINO, apart from being the first handheld device suitable for office-based practice, are lack of need to calibrate (a quality-control procedure confirms reliability) and the fact that one valid F_ENO measurement is sufficient (vs two required for the NIOX). The shelf life is 3.5 years from date of manufacture or 1500 uses, and measurement range is 5 to 300 ppb (lowest detection limit, 5 ppb). Results can be printed in all the models, although none has the ability to export data to external electronic medical record systems.

Studies have validated the reliability and correlation [11] of the NIOX MINO with the current standard NIOX in patients age 6 years and older presenting to an allergy and asthma clinic [12]. Additional feasibility studies have demonstrated that F_ENO monitoring is useful for asthma screening in young adults using the NIOX MINO [13•]. The NIOX MINO's costs are $2500 for the unit, $1750 for a test kit 100, $4000 for a test kit 300 (test kits include the sensor and mouth filters), $199 for data manager software, and $793 for a printer (Aerocrine, personal communication).

Another recent highlight has been the March 2008 FDA approval of a new desktop device designed for the physician's office: the Insight eNO System (Apieron, Menlo Park, CA). The Insight system uses a patented biosensor technology to provide safe, accurate, and noninvasive measurement of NO in a single breath [14]. It is reported to be highly accurate and easy to use, with comprehensive data management and analysis for customized patient therapy and 50 patient-specific smart cards to record and save F_ENO data (300 measurements per patient). It has a desktop unit that comes with a 6-month quality-control system proven for 18,000 test cycles between service intervals. The disposables include single-use sensors, filters that filter

carbon dioxide, and breath tubes. It is suitable for use in children older than 8 years and adults by trained operators in a physician's office or laboratory setting. The list price is $7500 for the monitor, and the disposable cost is about $15 per test (Apieron, personal communication).

F_ENO Coding and Reimbursement Issues

The American Medical Association current procedural terminology category 1 code has been assigned to exhaled NO. The current procedural terminology lists the code 95012 for NO expired gas determination, effective January 2007 [9••]. The Centers for Medicare and Medicaid Services reimbursement for exhaled NO is approximately $19, with fees ranging from $16 to $40 for other insurance carriers. Reimbursement from commercial insurers is variable, with some carriers classifying the test as investigational, experimental, or unproven and not reimbursable, a decision supported by an internal Blue Cross and Blue Shield Association Technology Evaluation Center report that is available to the public.

Offline Measurement of F_ENO

Offline measurement denotes collection and storage of a breath sample in a reservoir from which NO is subsequently measured. Offline collections are performed in infants and young children, all in clinical and research settings [7]. A recent study showed that F_ENO measurements using this methodology could distinguish subgroups of preschool children with respiratory symptoms [15••]. Wheezy children younger than 4 years old with a stringent asthma predictive index had elevated F_ENO levels compared with children with recurrent wheeze and a loose asthma predictive index or children with recurrent cough. Recent modifications of offline devices include visual feedback/incentives appropriate for young children and an indicator of proper inhalation of NO-free air [16•].

Reference F_ENO Levels

It has been challenging to establish normal healthy population values for F_ENO. A study of more than 200 nonsmoking adults found a range of 2.6 to 28.8 ppb in men and 1.6 to 21.5 ppb in women [17]. These data, coupled with those of Travers et al. [18], who ratified that men have an average of 25% higher F_ENO values than women, suggest the need for gender-specific norms. A study of more than 400 children between 4 and 17 years of age showed a mean value of 9.7 ppb at 4 years and 25.2 ppb in older children, hinting that F_ENO levels increase with age [19]. Values generally are between 5 and 35 ppb in healthy adults and 5 and 25 ppb in children. F_ENO levels increase with increasing height (change in F_ENO from 7 to 14 ppb with change in height from 120 to 180 cm) [20] and with race (healthy Chinese had higher levels compared with whites). Reference values for healthy, nonsmoking blacks also have been established recently [21•]. How body mass index affects F_ENO levels is also variable, with both increased [22] and decreased levels [23] reported in adults and no significant relationship noted in children [24].

Although airway inflammation, asthma, and atopy are major causes of elevated F_ENO, other factors influencing F_ENO levels have been reviewed recently [9••,25]. Factors causing an increase include albuterol (when a patient is taking inhaled corticosteroids), allergic rhinitis, eczema in nonasthmatic infants and toddlers (ambient NO levels affect peak, not plateau) [26], breath-holding, bronchiectasis, exacerbation of chronic obstructive pulmonary disease, ingestion of nitrate-containing foods (eg, lettuce and radishes), liver cirrhosis, lung transplant (acute rejection), nasal NO contamination, primary lung cancer, rhinovirus and upper respiratory tract infection, systemic lupus erythematosus, and tuberculosis. There is mild diurnal variation in F_ENO levels, with lower levels in the morning compared with the afternoon, although the day-to-day reproducibility is maintained. Factors that decrease F_ENO values include spirometric maneuvers, sputum induction, alcohol consumption, bronchoprovocation studies, cigarette smoking (active and passive), ciliary dysmotility syndrome, cystic fibrosis, diffuse alveolar hemorrhage, exercise 30 minutes before testing, and HIV infection. Factors that have not been reported to elevate F_ENO levels include albuterol in inhaled corticosteroid–naive patients, caffeine, long-acting bronchodilators, and stable chronic obstructive pulmonary disease [9••].

Genetics variations, including NOS polymorphisms, can affect baseline F_ENO levels, causing them to remain persistently elevated or low. Genetic and environmental influences on F_ENO levels and airway responsiveness in 377 adult twins were studied recently [27•]. Genetic effects accounted for 60% of variation in F_ENO, family environment contributed to 20% of variation in airway responsiveness, and nonshared environment contributed to the rest. The association between F_ENO and airway responsiveness ($r = 0.14$; $P = 0.006$) was due largely to the presence of common genetic factors.

Reference F_ENO Values in Populations With Asthma

After the seminal publication by Alving et al. [3], many studies have confirmed elevated F_ENO levels in patients with asthma. In general, the levels appear to be elevated twofold to fourfold compared with matched controls and tend to be between 25 and 80 ppb, although much higher values also have been reported in uncontrolled asthmatic patients. Despite the reduction in F_ENO levels due to active smoking, levels in asthmatic smokers tend to

be higher than in healthy smokers, suggesting that F_ENO may still be a useful marker of inflammation in smokers. The impact on F_ENO levels of variable amounts of passive smoke exposure experienced by children in real-life situations is controversial [28]. Atopy and airway hyperresponsiveness do increase F_ENO levels, even when the patient seems to be asymptomatic. Anti-inflammatory treatment reduces levels of F_ENO in asthma, with the response to corticosteroids being rapid (< 1 week, possibly 6–48 hours) and dose dependent, with a plateau of about 500 µg/d of beclomethasone [8,29]. Antileukotrienes also reduce levels, although to a lesser extent [2]. Use of short-acting and long-acting β_2 agonists generally does not affect F_ENO levels, as any effect is transient [30]. Some preliminary data suggest that omalizumab reduces F_ENO levels to a similar degree as inhaled corticosteroids [31]. In children with seasonal allergic rhinitis, one study found no difference in F_ENO between patients treated for two seasons with immunotherapy (IT) to grass pollen and those receiving placebo [32]. However, the authors found a significant increase in F_ENO in children receiving rush IT compared with traditional IT. In the rush IT group, baseline F_ENO was 12.6 ppb. This rapidly rose to 17.7 ppb at week 2. The elevated levels persisted until week 8 and then dropped below baseline to 8.9 ppb at week 12 ($P = 0.038$). These changes were not seen in the traditional IT group, and the difference between the two groups was most marked at week 4 ($P = 0.014$) [33].

Value of F_ENO as an Inflammometer

The value of F_ENO in asthma can best be summarized as its service as a resolute proxy, noninvasive marker of eosinophilic airway inflammation that correlates with eosinophils in blood, sputum, mucosa, and bronchoalveolar lavage [34]. Its exquisite sensitivity to changes in anti-inflammatory therapy (particularly inhaled corticosteroids) [35] and degree of inflammation (not necessarily in parallel to changes in sputum eosinophils) enables it to be a barometer to titrate and individualize therapy [36]. It also may serve to classify asthmatic patients into phenotypes, as demonstrated by Silkoff and colleagues [37], who found that elevated F_ENO measurements identified a subgroup of patients with severe steroid-refractory asthma and persistent eosinophilia. Fitzpatrick et al. [38••] corroborated this concept in finding that "severe asthma in children is characterized by a relatively narrow spectrum of derangements that included marked atopy and increased F_ENO."

Suggested Use of F_ENO in Clinical Settings

It is clear that F_ENO value is not just a standalone parameter, but it also can be extremely useful when juxtaposed against the clinical context. Factors that need to be weighed include whether the patient is known to have asthma, whether it is used to screen or diagnose asthma, the status of his or her symptoms, whether he or she is atopic and whether this is his or her allergic season, whether he or she is on therapy and the nature of the therapy, and what his or her previous levels were. Therefore, selection of appropriate cutoff values customized to the clinical scenario may be preferable to using normative values [39]. Also, establishing individual personal best with F_ENO—akin to how peak flow readings are used—along with individual serial measurements may be the best way to use F_ENO in clinical practice. Within the context of the previously mentioned caveats, the following scenarios may be best suited for effective use of F_ENO (Table 1).

Diagnosis of asthma

F_ENO levels greater than 20 to 35 ppb suggest the presence of asthma in a steroid-naïve symptomatic patient, whereas lower levels suggest absence of eosinophilic inflammation [9••,40]. In such a case, alternative diagnoses may need to be considered (eg, neutrophilic asthma or other differential diagnoses) [41•]. A recent report also suggested that the cutoff point of 20 to 25 ppb may be useful in the screening of asthma [13•].

Prediction of response to inhaled corticosteroids

F_ENO levels greater than 45 to 50 ppb may predict steroid responsiveness and serve to guide controller therapy [36]. Taylor [41•] suggests that an F_ENO greater than 50 ppb in adults and greater than 35 ppb in children, combined with objective evidence of reversible airway obstruction, indicates that asthma is very likely, as is a positive response to a trial of steroids. Elevated F_ENO greater than 25 to 50 ppb in children may indicate forced expiratory volume in 1 second response greater than 7.5% with inhaled corticosteroids compared with leukotriene antagonists [42,43••]. An elevated F_ENO greater than 38 ppb in patients with chronic cough is predictive of a response to inhaled corticosteroid therapy [44].

Evaluation of response to inhaled corticosteroids

A decrease of at least 20% of previous F_ENO levels may indicate efficacy of controller medication [8].

Titrating optimal dose of inhaled corticosteroids and dose reduction

Levels less than 35 ppb can suggest optimal asthma control in an asthmatic patient receiving therapy [45]. Low F_ENO levels (< 25 ppb) in an asymptomatic individual indicate that inhaled corticosteroid dose may be reduced or even withdrawn altogether [41•].

Predicting loss of control and relapse

An increase of F_ENO of 60% between visits was predictive of impending loss of asthma control [46]. F_ENO

Table 1. Suggested use of F_ENO in clinical asthma management

Applications	Supportive data	Reference(s)
Diagnosing asthma •When used in conjunction with other parameters •In individuals who do not meet criteria for reversibility •Normal values are 5–20 ppb (up to 15 ppb in children)	80% correct diagnosis in patients 8–75 y old using cutoff of 20 ppb 80% correct diagnosis in patients 4–8 y old using cutoff of 10 ppb	Smith et al. [40], Malmberg et al. [55]
Selecting a therapeutic agent: predicting response to ICS	F_ENO > 47 ppb highly indicative of response in patients with nonspecific symptoms Median exhaled NO level of 54 ppb was the significant cut point that recognized an FEV_1 improvement ≥ 7.5% with ICS but not LTRA in children Exhaled NO level of > 25 ppb at baseline was associated with increased likelihood of FEV_1 improvement ≥ 7.5% (OR, 2.8; $P < 0.05$)	Smith et al. [36], Szefler et al. [42], Zeiger et al. [43••]
Evaluating response to ICS	Reduction of at least 20% in unstable patients indicates efficacy of anti-inflammatory treatment	Silkoff et al. [8]
Titrating optimal dose of ICS	F_ENO cutoff goal < 35 ppb Once the clinical symptoms and F_ENO are stable, steroid dose can be gradually reduced to the point at which F_ENO starts to rise	Smith et al. [45]
Predicting loss of control and predicting asthma relapse	If the F_ENO level increases 60% between visits, this has a PPV > 80% of an imminent decrease in asthma control Pediatric: F_ENO > 35 ppb; PPV: 53%; NPV: 91% When asymptomatic children in clinical remission stopped taking steroids, F_ENO > 49 ppb 2–4 wk later was an effective predictor of asthma relapse	Jones et al. [46], Pijnenburg et al. [47], Zacharasiewicz et al. [48]
Identifying nonadherence/ noncompliance	Elevated F_ENO level (> 35 ppb) in a patient taking maintenance doses of ICS indicates that the patient is not prescribed adequate amounts of the right therapy or is not taking it correctly	Delgado-Corcoran et al. [49]

F_ENO—fractional concentration of exhaled NO; FEV_1—forced expiratory volume in 1 second; ICS—inhaled corticosteroids; LTRA—leukotriene receptor antagonist; NO—nitric oxide; NPV—negative predictive value; OR—odds ratio; ppb—parts per billion; PPV—positive predictive value.

measurements are also helpful when considering stopping inhaled corticosteroid therapy if asthma appears to be in remission. Pijnenburg et al. [47] addressed this issue in a study of 40 children with stable asthma in whom inhaled corticosteroid treatment was withdrawn. The levels of the nine relapsers rose steadily during the 24-week post-withdrawal period, from a mean F_ENO at baseline of 14.8 ppb to 40.8 ppb at 4 weeks, compared with 10.5 ppb to 15.9 ppb, respectively, in the nonrelapsers ($P = 0.01$) [47]. Optimum positive and negative predictive values for subsequent relapse were obtained at an F_ENO of 49 ppb, a level notably similar to the cut point for "steroid responsiveness" in the study by Smith et al [36]. Zacharasiewicz et al. [48] also determined that the absence of sputum eosinophils, with simultaneously low F_ENO levels, predicted successful withdrawal of inhaled corticosteroid therapy in children.

Identification of noncompliance and other comorbid factors

Elevated F_ENO levels (eg, > 35 ppb in patients taking maintenance dose of inhaled corticosteroids) suggest that there may be atopy, persistent airway inflammation, or nonadherence to therapy [9••,49]. However, high F_ENO levels (> 45–50 ppb) in asymptomatic individuals do not necessarily imply the need for clinical intervention and should be interpreted strictly with reference to the clinical history.

Unresolved Issues: Use of F_ENO-Based Treatment Algorithms in Asthma Management

Two biomarker-based studies confirmed that treatment algorithms based on induced sputum eosinophil counts result in significant improvements in asthma control compared with a strategy guided by symptoms and lung function [50]. Given the ease and noninvasive nature of obtaining F_ENO measurements, a few researchers attempted to study the same thing using F_ENO-based algorithms. In a study by Shaw and coworkers [51••], 118 patients with asthma were randomized to single-blind treatment with inhaled corticosteroids administered according to British Thoracic Society guidelines (n = 60) or an F_ENO-driven treatment strategy (n = 58) involving titrating inhaled corticosteroid doses according to F_ENO concentrations. Unfortunately, the F_ENO-based strategy did not result in a significant reduction in asthma exacerbations (estimated exacerbation frequency [mean ± SD], 0.33 ± 0.69 vs 0.42 ± 0.79 per patient per year in the F_ENO and control groups, respectively; P = 0.43). A lack of power was a weakness of the study, although there was no significant trend toward improved asthma control in the F_ENO group. The final daily inhaled corticosteroid dose, however, was significantly lower in the F_ENO group (557 vs 895 µg; P = 0.028), although there was a nonsignificant 11% increase in overall inhaled corticosteroid administration in the F_ENO group (95% CI, 17% to 42%; P = 0.40).

An appropriately powered study by Smith and colleagues [45] reported that by using F_ENO to guide management, the maintenance dose of inhaled corticosteroids could be significantly reduced by more than 40%. Despite the reduction in dose, the exacerbation frequency was lower (by 45%)—but not significantly—in the F_ENO strategy group [45]. Another study compared the strategy of using symptoms alone with that of symptoms plus F_ENO levels to guide treatment in children with asthma over a year [52]. Although the study was not powered to demonstrate differences in exacerbation rates (though there were fewer exacerbations, 18 vs 8), it demonstrated that airway hyperresponsiveness was reduced by 2.5 doubling doses in the F_ENO strategy group compared with 1.1 doubling doses in the "symptoms" group.

A recent Cochrane meta-analysis of these studies [53•] concluded the following:

> Tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide in comparison to clinical symptoms was carried out in different ways in the four studies that were found, and the results show only modest differences. The role of utilizing exhaled nitric oxide to tailor the dose of inhaled corticosteroids is currently uncertain.

It recommends performing parallel multicenter, randomized, controlled trials in adults and children that take into consideration other factors that may affect F_ENO levels (eg, atopy), *a priori* determination of high versus low doses of inhaled corticosteroids, eosinophilic versus noneosinophilic asthma, inclusion of outcomes such as exacerbations, subjective measures such as scores for asthma control and quality of life, objective measures (eg, forced expiratory volume in 1 second), and cost analysis for each subgroup.

In a thoughtful editorial, Taylor [54••] reflects that key issues revolve around study design and choice of cutoff points, which are critical when designing such studies. The lower the F_ENO cut point, the higher the mean inhaled corticosteroid dose requirement will be, and vice versa, with consequent differences in the resulting exacerbation rate. The significance of cut points applies equally to the control groups. The thresholds at which symptoms and peak flows are set to prompt treatment change in the control group also influence study outcomes. Other issues, such as gender differences in F_ENO levels and lack of agreement between F_ENO levels and simultaneous sputum eosinophil counts, may affect cutoff values. Unlike sputum eosinophils, a zero value for F_ENO cannot be achieved, not even with optimum anti-inflammatory treatment, as "normal range" for F_ENO is influenced by constitutional, environmental, and pathophysiologic factors [54••].

Conclusions

Exhaled NO measurements provide hitherto-unmeasured invaluable insight into the status of eosinophilic airway inflammation in children and adults with asthma. Validated, FDA-approved, easy-to-use, office-based tests are available to perform these measurements. Use of these tests in a longitudinal and personalized manner using individualized norms supplements other assessments of asthma diagnosis and control and should be considered an integral element of office-based asthma management.

Disclosure

Dr. Dinakar has served on the advisory board and the speakers' bureau and received honoraria from Aerocrine.

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