

A Perspective on Fractional Exhaled Nitric Oxide Measurement for Adherence Monitoring



Myron Zitt, MD^{a,b} *Stony Brook and East Meadow, NY*

Recent data indicate that the annual asthma mortality rate in the United States is on the rise, increasing from 3388 in 2009 to 3651 in 2014.^{1,2} Although about 10 people in this country die from asthma daily, exacerbations leading to hospitalization rates of nearly 0.5 million per year and emergency room visits of 1.9 million per year have contributed to the high cost of asthma care, estimated in 2009 at \$56 billion per year. A national telephone survey, Asthma Insight and Management, using an algorithm based on National Asthma Education and Prevention guidelines to classify current control, demonstrated that although most patients and their health care providers believed that their asthma was well controlled, an alarming 71% of adolescent and adult patients 12 years or older ($n = 2500$) had very poorly or not well-controlled asthma.³ Nonadherence to inhaled corticosteroid (ICS) therapy, commonly reported to be from 30% to 70%, is a major cause of poor control, which, in turn, is associated with increased asthma exacerbations and the frequent utilization of acute health care resources that impacts significantly on health care costs and asthma mortality.⁴ Adequate assessment of adherence would improve outcomes by allowing practitioners to determine whether uncontrolled asthma symptoms are due to intrinsic disease severity, the inadequacy of treatment, or a failure to follow prescribed recommendations.⁵ Although various methods of measuring ICS adherence have been studied, including patient and physician records, pharmacy refill records, canister weights, and electronic monitoring, none can be considered a reliable “criterion standard.”^{5,6}

Fractional exhaled nitric oxide (FENO) is a noninvasive, quick, simple, and reproducible marker of T_H2 -driven eosinophilic airway inflammation in allergic asthma. IL-4 and IL-13 (but not IL-5) upregulate epithelial cell–inducible nitric oxide synthase via signal transducer and activator of transcription 6, leading to the corticosteroid-sensitive increased production of exhaled nitric oxide in patients with T_H2 -driven airways inflammation, characteristic of allergic asthma.⁵

Because of its heterogeneity, characterized by multiple phenotypes and endotypes, asthma is increasingly being recognized as a syndrome rather than a single disease entity.⁷ The American Thoracic Society (ATS) strongly recommends the use of

FENO as an aid in phenotyping patients with asthma, identifying those who are likely to respond to ICS therapy when FENO is high, and those who are unlikely to respond to ICS therapy when FENO is low. As levels decrease within days after corticosteroid treatment, and increase rapidly after steroid withdrawal, FENO should be ideal in monitoring patient adherence to corticosteroid therapy in patients with allergic asthma.^{8,9}

To test his hypothesis, Beck-Ripp et al¹⁰ evaluated adherence with inhaled budesonide therapy in 54 steroid-sensitive children with asthma, ages 6 to 16 years, by determining baseline FENO levels and following sequential changes with or without ICS therapy. FENO was able to differentiate between children briefly treated with or without steroids. Because there was a strong inverse correlation between FENO and patient compliance, the authors suggested that FENO “may thus be a valuable parameter to monitor adherence to steroids.”

To further determine whether FENO could be a useful proxy measure to assess adherence to ICS controller therapy, Klok and Brand,¹¹ in this issue of the journal, performed a 1-year observational longitudinal study of 60 children (mean age, 8 years) with persistent asthma, who were generally well controlled with low to moderate doses of inhaled fluticasone propionate. ICS adherence was assessed, using Smarthalers or SmartDisk devices, to determine a value, on the basis of the ratio of device-recorded to prescribed ICS doses. This value was then correlated with random FENO values, determined at follow-up visits, after 6 to 12 months. A median FENO level of 14 ppb was recorded (a FENO level of >25ppb was determined to be a measure of non-adherence). Data were analyzed on the basis of findings from the “overall population” of 60 children and separately, from the 44 of 60 who were sensitized to at least 1 aeroallergen and were thus determined to have “atopic asthma.” Based on the study protocol, several conclusions were drawn. (1) The “random assessment of FENO appears to be a poor predictor of adherence in the overall population of children being prescribed ICS therapy” and (2) the “results of the subgroup analysis of children with poorly controlled atopic asthma, characterized by eosinophilic inflammation, suggest that FENO might be a useful marker of non-adherence in such patients.”

Up to 80% of children with asthma have an “early onset” or allergic phenotype, with T_H2 -producing cytokines, including IL-4, IL-5, and IL-13, promoting corticosteroid-sensitive eosinophilic airway inflammation.⁶ This percentage is lower in adults in whom non- T_H2 asthma may affect 50% or more of corticosteroid-naïve individuals.^{7,12} IL-5 production and resulting eosinophilic inflammation can be representative of different phenotypes because it can be driven by either of 2 cells, (1) allergen-specific T_H2 cells characteristic of early onset allergic asthma or (2) allergen-independent (nonallergic) innate lymphoid cells, as can be present in late-onset eosinophilic

^aDepartment of Medicine, Division of Allergy/Immunology, State University of New York, Stony Brook, NY

^bAdult Allergy Clinic, Nassau University Medical Center, East Meadow, NY

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Corresponding author: Myron Zitt, MD, Mid Island Allergy Group, 1171 Old Country Road, Suite 5, Plainview, NY 11803. E-mail: Myron.zitt@gmail.com.

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asthma and in aspirin-exacerbated respiratory disease.¹³ Thus, eosinophilic airway inflammation can exist in the absence of allergic asthma and elevated FENO levels. Neither children nor adults with non- T_H2 asthma would be expected to have elevated FENO levels.

As the Klok and Brand study measured FENO levels at random time points in relatively well-controlled patients, of whom about 25% had no evidence of allergic asthma, it comes as no surprise that values were a poor predictor of adherence. FENO levels would not change in non- T_H2 asthma regardless of adherence. Because most patients were well controlled, FENO would not be elevated, even if some of the allergic patients were nonadherent. In this study, mean FENO was a low 14 ppb even though three-fourth were said to have allergic asthma. In truth, because asthma symptoms and the degree of airway inflammation are variable, on the basis of ATS recommendations, some of the study patients with low FENO levels might have been able to taper down and perhaps discontinue ICS therapy.^{8,12}

Most importantly, in the subgroup of children with poorly controlled allergic asthma, Klok and Brand observed a significant correlation between FENO levels and ICS adherence. Several additional studies using FENO measurements at random time points to monitor ICS adherence support these observations. Koster et al¹⁴ reported that increased FENO levels of more than 25 ppb, in children prescribed ICS, were associated with reduced adherence.

More recently, McNicholl et al¹⁵ evaluated adult patients with poorly controlled asthma, with T_H2 -driven inflammation, characterized by FENO levels of more than 45 ppb at random time points while taking ICS.¹⁵ Poor adherence was confirmed in these patients by demonstrating a fall in FENO levels, after 7 days of directly observed ICS treatment.

One might coordinate the important observations of Klok and Brand with the recommendations of the ATS to conclude the following:

1. The measurement of FENO in the initial evaluation of symptomatic asthma patients can, when elevated, aid in identifying patients with a T_H2 -driven eosinophilic allergic phenotype and likely responsiveness to ICS.
2. In patients who do not exhibit elevated FENO levels when symptomatic at their initial evaluation, it is neither reasonable nor cost-effective to measure random or sequential FENO levels. FENO levels will not significantly change in these patients even if they are ICS nonadherent.
3. In those patients, with T_H2 -driven asthma, treated with appropriate ICS therapy, changes in FENO levels with sequential FENO measurements can confirm ICS responsiveness and adherence.
4. In patients with poorly controlled allergic asthma, elevated FENO levels, when measured at random time points, or rising levels with sequential measurements, suggest ongoing T_H2 -driven eosinophilic inflammation, which could be indicative of suboptimal patient ICS adherence or ICS dosing, ongoing exposure to proinflammatory allergens, or less often, steroid resistance. This is consistent with the very important subgroup observations of

Klok and Brand because health care providers can use this information to improve asthma outcomes through patient education and adjustments in therapy.

5. In patients with well-controlled asthma, the random measurement of FENO without baseline levels provides no information regarding adherence and is not recommended as reported by Klok and Brand.
6. FENO levels at random or sequential time points, in poorly controlled non- T_H2 asthma patients, will not change significantly regardless of the presence or absence of ICS nonadherence. Thus, randomly measured low FENO levels provide no information regarding adherence and measuring FENO levels in this group is not recommended.

One would urge that patient selection for future asthma studies take patient phenotype into consideration. With this in mind, measuring FENO to evaluate adherence appears to be of value as noted by Klok and Brand in patients with T_H2 -driven allergic asthma, but of little value in monitoring those with non- T_H2 -driven inflammation.

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