

although data for patients with asthma did not meet statistical significance and asthma was not listed as a predictor of admission in our study population, we did see a difference in admission rates between the patients with asthma and the patients without asthma groups.

As Mulla and Simon stated in their letter, “A comparison group of patients with anaphylaxis who were not hospitalized would be needed to allow the calculation of a confounder-adjusted measure of association (eg, an odds ratio for the relationship between asthma and anaphylaxis hospitalization after controlling for age, race, sex, and comorbidities).” Given our differences in examining predictors of hospitalization in those patients with a diagnosis of anaphylaxis and the exclusion of asthma in our final recommendations, our data would indicate that physicians maintain a low threshold for admission in patients presenting with our risk factors for admission: specifically, a patient presenting with an anaphylactic episode involving multiple organ systems including gastrointestinal symptoms after exposure to an ingested allergen and a history of anaphylaxis.

Luz Fonacier, MD*

Ryan Steele, DO†

Mark Davis-Lorton, MD*

Marcella Aquino, MD*

*Section of Allergy and Clinical Immunology

†Department of Medicine

Winthrop-University Hospital

Mineola, New York

Lfonacier@winthrop.org

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Should exhaled nitric oxide be part of routine asthma management?

To the Editor: In view of the American Thoracic Society Guidelines, which recommends the use of fractional exhaled nitric oxide (FeNO) in the management of asthma, a position supported in a joint American College of Asthma, Allergy and Immunology/American Academy of Asthma, Allergy and Immunology statement, we take issue with the context and conclusions of the recent perspective by Sami Bahna regarding the routine use of FeNO.^{1–3} The author offers only a selective and limited review of the literature and casts a contrasting negative light on this procedure.

Airway inflammation is a key element in asthma dysfunction, and its control remains a proper goal of good asthma care. This is supported by existing guidelines.⁴ The traditional tools commonly used for patient assessment are not valid proxies for airway inflammation. Induced sputum for inflammatory cells and the measurement of FeNO are, with the latter being available using simple tools that provide rapid and accurate measurements in the context of clinical care.

The oft quoted studies of Pijnenburg, Fritsch, Szefer, Smith, and Shah suffer from design flaws that limit their interpretation and translation into clinical care.^{5–9} This was clearly described by the hallmark article on ASTRAL studies by Gibson, not cited by Bahna.¹⁰

Bahna cites that the study by Szefer et al⁷ failed to demonstrate improved outcomes using FeNO. Yet, he ignores that this study showed that fewer prednisone bursts were required by the FeNO-treated group and that a subset of patients with obesity, high eosinophil counts, and atopy showed a larger decrease in days of asthma symptoms when managed with FeNO guidance.

In citing a paper by Gelb et al,¹¹ Bahna fails to acknowledge their findings that a high FeNO and a low forced expiratory volume in 1 second when considered together are the best predictors of exacerbations.¹¹ The use of composite markers to arrive at better decision-making was 1 of the recommendations made by Gibson.¹⁰

The point made by Khalili et al¹² is inaccurately stated. The focus of the article is that instruments assessing asthma and its control do not correlate with FeNO, because this biomarker of inflammation is reflecting a different perspective of asthma from guideline measures. This is a positive characteristic of FeNO measurements, not a negative, as implied.

A Cochrane review¹³ also recognizes significant limitations in the studies on which it based its conclusions (Smith, Shah, Pijnenburg, Fritsch), in that these studies had significant variations in management schemes, with differences in control arms, management arms, FeNO cut points, and symptom cut points for decision making, and methods of measuring FeNO. Several of the articles in this review are cited by Bahna to support his perspective.^{5,6,12,13}

Another omission in this perspective is a paper by Powell et al¹⁴ that clearly showed that management using an FeNO-driven protocol during pregnancy resulted in a significant reduction in exacerbations as well as improved neonatal outcomes for infants born to the women so managed.

The use of FeNO measurements has clinical value far beyond simply raising or lowering inhaled corticosteroid (ICS) doses. These include supporting the diagnosis of asthma, alerting the health care provider to non-asthma conditions masquerading as asthma, and addressing the need for an extended differential diagnosis, such as the recognition of eosinophilic bronchitis. Of equal importance is identifying asthma phenotypes most likely to respond to ICS, alerting the clinician to either inadequate or excessive ICS dosing, patient nonadherence to ICS, poor delivery of ICS doses via improper patient technique, or improper patient–device matching. The uncovering of important and often unappreciated allergen exposure and the early recognition of patient loss of asthma control are also of great benefit in achieving optimal asthma management.

In closing, we believe that it is a mistake to view FeNO as a replacement for the traditional tools used to assess asthma control or to insist that it correlate with them. It is not and was never intended to do so. FeNO is a complementary tool that provides a clinical perspective of airway inflammation that can positively impact clinical decision-making. As such, we believe that it should assume its rightful place amongst the tools used to provide optimal asthma care.

Neal Jain, MD

Peter Boggs, MD

Myron Zitt, MD

jain7@gmail.com

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Author response

To the Editor: The Correspondence by Jain et al is not surprising. My Perspective article,¹ being criticized, consisted merely of a concise summary of the pathophysiology of nitric oxide in health and disease, followed by a summary of studies on fraction exhaled nitric oxide (FENO) measurement relevant to the diagnosis or assessment of asthma. It included one study² I participated in, and its findings were consistent with many previously or subsequently published studies that were summarized in the Perspective article.

Jain et al do not want to accept the findings of numerous well-designed studies that were carried out in academic institutions by experienced neutral investigators, peer-reviewed by experts, and published in prestigious scientific journals. They claim “flaws” in those studies and cite support by an individual’s opinion on methodological discrepancies,³ but not by studies. It is indisputable that FENO levels overlap between healthy subjects and patients with asthma; and that numerous factors, including common comorbidities of asthma, influence FENO level upwards or downwards.^{1,4} Information is accumulating to indicate that FENO seems to be a biomarker of general atopy, which includes atopic asthma.^{5–7}

The large number of studies summarized in the Perspective provided overwhelming evidence that FENO is not superior to currently used asthma assessment methods and does not optimally reflect the level of asthma control. In an additional study, Visser and Brand⁸ followed, for 12 months, 103 children (6–16 yr of age) with asthma controlled on daily inhaled corticosteroid therapy. They noted that FENO level did not predict asthma exacerbation, and the levels in children who had exacerbations markedly overlapped with those of children who had no exacerbations.

It is true that the traditional clinical tools used for asthma assessment are not good proxies for airway inflammation, but FENO level is not a perfect proxy either because eosinophilic inflammation and FENO levels do not always respond identically to treatment.⁹ Jain et al claim support from the ATS Guidelines.⁴ The latter “recommend the use of FENO in the diagnosis of eosinophilic airway inflammation”, but it clearly admits “low quality of evidence” for recommending “the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation” or “the use of FENO in monitoring airway inflammation in patients with asthma”, as well as for some other recommendations or suggestions relevant to interpreting FENO levels.

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In addition to the studies summarized in the Perspective, a few new studies were published later with similar conclusions. Calhoun et al¹⁰ carried out a multicenter study on adults with mild to moderate asthma controlled on low doses of inhaled corticosteroids and were followed for 9 months. The dose of inhaled corticosteroids was adjusted every 6 weeks either according to FENO level or according to the physician’s assessment. The rate of clinical worsening was the same in the two groups; 20% in the FENO group and 22% in the physician’s assessment group.

To the best of my knowledge, most academic centers have not adopted FENO measurement in routine asthma management. In our eagerness for better diagnostic or therapeutic modalities, prudence dictates to be objective in watching the new then embrace what proves optimally reliable. Ignoring the evolving scientific data would be like “*I made up my mind, don’t confuse me with the facts.*”

Sami L. Bahna, MD, DrPH
Allergy & Immunology Section
Louisiana State University Health Sciences Center
Shreveport, Louisiana
SBAHNA@LSUHSC.EDU

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