



Contents lists available at ScienceDirect



Impact of exhaled nitric oxide measurements on treatment decisions in an asthma specialty clinic

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ARTICLE INFO

Article history:

Received for publication April 10, 2014.

Received in revised form May 15, 2014.

Accepted for publication June 20, 2014.

ABSTRACT

Background: Asthma management in an outpatient setting is best accomplished by clinical evaluation coupled with spirometry and symptom evaluation, but these assessments do not provide information about airway inflammation. Exhaled nitric oxide (fraction of exhaled nitric oxide [FeNO]) measures T-helper cell type 2–mediated airway inflammation and may be a useful adjunct in asthma management.

Objective: To determine whether the use of FeNO in the specialist management of asthma results in more effective and cost-effective treatment decisions.

Methods: Fifty subjects 7 to 60 years old with established asthma participated in this observational study. Subjects were evaluated by clinical examination, spirometry, and symptom assessment using the Asthma Control Test, and clinicians estimated airway inflammation and made treatment decisions based on these assessments. Then, FeNO was measured, and changes in therapy based on FeNO levels were documented. The estimated cost impact of using FeNO was calculated presuming ongoing FeNO use in patient management.

Results: Without FeNO, the clinician's assessment of airway inflammation was incorrectly classified in 50% of subjects. FeNO results substantially altered treatment decisions in more than one third of subjects, notably medication augmentation in 10 (20%) and medication decreases in 8 (16%). Use of FeNO in addition to standard of care was estimated to save \$629 per subject per year.

Conclusion: Measurement of FeNO augments routine clinical assessment of asthma by measuring airway inflammation. Knowledge of FeNO affects medication treatment decisions to augment or decrease pharmacotherapy, which has important long-term asthma management implications, most notably the potential to lower the costs and morbidity associated with asthma exacerbation.

Trial Registration: ClinicalTrials.gov identifier NCT01729247.

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Introduction

Management of asthma in an outpatient setting has traditionally been accomplished with clinical evaluation, spirometry, and symptom evaluation,^{1–3} but these assessments do not provide information about ongoing airway inflammation, which is a key and necessary factor to achieving desired asthma control.

Before the availability of a device to measure the biomarker exhaled nitric oxide, assessment of airways inflammation was invasive, required specialized equipment, and was time consuming, which made it impractical for use in most primary care or specialty care settings. Fractional exhaled nitric oxide (FeNO) is recognized as a noninvasive point-of-care tool for the assessment of allergic airway inflammation in patients with suspected but undiagnosed asthma. FeNO is useful for monitoring response and adherence to inhaled corticosteroid (ICS) therapy, guiding adjustments in ICS dosage,^{2,4–9} and assessing the risk of worsening asthma.^{10,11}

Although measurement of FeNO is recommended for use in the management of asthma, the impact of FeNO levels on treatment decisions made by asthma specialists has not been well documented. The objective of the present study was to determine the ability of asthma specialists to assess airway inflammation without the aid of FeNO levels and to determine the impact of

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Disclosure: Dr Brooks has consulted for Aerocrine. The remaining authors have nothing to disclose.

Funding: Aerocrine, Inc.

Previous Presentations: European Respiratory Society, 2013 (poster); American College of Allergy, Asthma and Immunology, 2013 (poster); and American Academy of Allergy, Asthma and Immunology, 2014 (poster).

<http://dx.doi.org/10.1016/j.jana.2014.06.013>

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measuring FeNO levels on subsequent asthma treatment decisions and cost of care.

Methods

This study was an observational, single-center, single-visit study conducted at an outpatient asthma and allergy specialty clinic in November 2012. Fifty subjects 7 to 60 years of age who were established patients and had a current diagnosis of asthma, but in whom FeNO would not have been previously measured, were approached to participate in the study at their clinic appointment (scheduled for routine or acute problems). Subjects were excluded if they had an established diagnosis of chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, obliterative bronchiolitis, ciliary dyskinesia, postviral bronchial hyperresponsive syndrome, or vocal cord dysfunction. Subjects also were excluded if they had at least a 10-pack-year history of smoking or had participated in an investigational study in the past 30 days. It is unknown whether any of the participating subjects had previously been documented as having bronchial hyperresponsiveness. The study was reviewed and approved by an appropriately constituted institutional review board.

After signing a written informed consent to participate (or assent for minor children), subjects performed spirometry, completed the Asthma Control Test (ACT),¹² and were examined by a health practitioner (physician or physician's assistant). After these assessments, a single FeNO measurement was obtained (NIOX MINO, Aerocrine AB, Solna, Sweden), but the FeNO results were not shared with the clinicians until after they had estimated the degree of airway inflammation and made treatment decisions based on the composite clinical picture using spirometry, ACT scores, and clinical examination. For each subject, the degree of airway inflammation was estimated as low (<25 ppb for ≥ 12 years of age or <20 ppb for <12 years of age), intermediate (25–50 ppb for ≥ 12 years of age or 20–35 ppb for <12 years of age), or high (>50 ppb for ≥ 12 years of age or >35 ppb for <12 years of age) as defined by the American Thoracic Society.² After estimating inflammation and documenting the planned treatment for each subject, the FeNO results were made available to the clinicians and they recorded how knowledge of the FeNO level affected their treatment decisions.

To estimate the potential impact of knowledge of FeNO on asthma management costs, a decision analysis was conducted to examine expected medical resource usage for patients managed with standard guidelines plus FeNO compared with patients managed with standard guidelines only. The model's framework and likelihoods of experiencing or not experiencing asthma exacerbations and of using various medical resources (eg, physician office visits, medications, emergency department visits) were drawn from the peer-reviewed literature.^{13–19} Mean hospital costs were based on the Healthcare Cost and Utilization Project's 2009 National Statistics for Asthma for principal diagnosis only. Costs associated with asthma diagnostic technologies and with FeNO measurements were based on the appropriate *Current Procedural Terminology* codes, and payment levels were calculated at 120% of Medicare 2013 national average allowable costs. The average cost of medications (rescue drugs, such as oral steroids and short-acting β agonists, and maintenance therapies including ICSs) was based on RedBook and medshealth.com. All cost estimates were updated to 2013 US dollars using the Consumer Price Index for Healthcare Products and Services.

Because this was an observational pilot study, there were no plans for formal statistical analyses. Collected data were summarized but not subjected to hypothesis testing.

Results

Fifty subjects were recruited into this study and all completed the study. There were no adverse events, and all subjects were able

to provide a FeNO measurement. The mean age was 35.1 years (range 7–60 years), 60% of subjects were female, and the mean forced expiratory volume in 1 second (FEV₁) was 85% of predicted (Table 1). The most commonly taken medications were short-acting β agonists (94%), anti-inflammatory treatment in the form of a long-acting β agonist combined with an ICS (40%) or a single-agent ICS (20%), and leukotriene receptor antagonists (16%).

Five clinicians, including 4 board-certified allergists and 1 nurse practitioner, evaluated 18, 7, 3, 8, and 14 subjects, respectively. Nearly all subjects (96%) were estimated by clinician appraisal to have low (68%) or intermediate (28%) FeNO levels, whereas only 4% of subjects were estimated to have a high FeNO value (Table 2). However, the actual classification was incorrect in half the subjects, resulting in a general underestimation of the degree of inflammation. Overall, there were 29 subjects (58%) with low FeNO, 10 (20%) with intermediate FeNO, and 11 (22%) with high FeNO. In the group of 11 subjects with high FeNO, 7 of 11 (63.6%) had ACT scores no higher than 19 (indicating less than optimal asthma control), 6 of 11 (54.5%) were not currently receiving ICS therapy, and 6 of 11 (54.5%) had normal lung function, defined as a predicted FEV₁ value higher than 80% (Table 3). Overall, mean and median FeNO values were higher in subjects with ACT scores no higher than 19 (40.3 and 18.0

Table 1

Baseline characteristics and current medications

	Per-protocol population (N = 50)
Age (y)	
Mean (SD)	35.1 (15.81)
Range	7–60
Female subjects, n (%)	30 (60)
Primary race, n (%)	
White	33 (66)
Black or African American	16 (32)
Other	1 (2)
Ethnicity, n (%)	
Not Hispanic or Latino	50 (100)
Height (cm)	
Mean (SD)	165.1 (11.0)
Range	122.4–183.4
Weight (kg)	
Mean (SD)	75.0 (19.0)
Range	25–119
BMI (kg/m ²)	
Mean (SD)	27.4 (6.2)
Range	17.2–44.2
Smoking status, n (%)	
Never smoked	35 (70%)
Current smoker	0
Past smoker	15 (30%)
Spirometry	
FEV ₁ (% predicted)	
Mean (SD)	85.2 (17.2)
Range	44–123
FEF _{25–75} (L/s)	
Mean (SD)	2.29 (1.10)
Range	0.50–5.22
FEV ₁ /FVC ratio (%)	
Mean (SD)	74.28 (9.91)
Range	52–92
Most commonly taken current asthma and allergy medications, n (%)	
SABA	47 (94)
ICS-LABA combination	20 (40)
H ₁ receptor antagonist	17 (34)
ICS	10 (20)
Antihistamine	9 (18)
Intranasal corticosteroid	9 (18)
Leukotriene receptor antagonist	8 (16)
Nasal decongestant	4 (8)

Abbreviations: BMI, body mass index; FEF_{25–75}, forced expiratory flow of 25% to 75%; FEV₁, forced expiratory volume in 1 second; FVC, force vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β agonist; SABA, short-acting β agonist.

Table 2

Airway inflammation: subjects categorized by clinical appraisal vs observed FeNO levels

Observed FeNO level of airway inflammation	Clinical appraisal of airway inflammation			
	Low	Intermediate	High	Total
Low	21 (42%)	7 (14%)	1 (2%)	29 (58%)
Intermediate	7 (14%)	3 (6%)	0	10 (20%)
High	6 (12%)	4 (8%)	1 (2%)	11 (22%)
Total	34 (68%)	14 (28%)	2 (4%)	

Abbreviation: FeNO, fraction of exhaled nitric oxide.

ppb, respectively) than in the group with scores higher than 19 (26.1 and 13.5 ppb). FeNO values also were higher in subjects with an FEV₁ no higher than 80% predicted (mean 41.1 ppb [median 24.0] vs 30.9 ppb [14.0] for those with FEV₁ >80% predicted) and higher in those not receiving ICS therapy (mean 46.4 ppb [median 23.0] vs 25.7 ppb [17.0] for those who were).

Asthma treatment changes were made by clinicians according to their experience and clinical judgment and there was no attempt to control or intervene in treatment choices. Asthma treatment changes were made in 18 subjects (36%) after FeNO measurement, including 10 subjects who had medication added or the dose increased and 8 subjects who had the medication discontinued or the dose decreased (Table 4). All subjects in whom medication was decreased or eliminated were on anti-inflammatory therapy, but all had low FeNO values (≤ 18 ppb) and somewhat discordant other indices, including largely normal lung function (FEV₁ >80% of predicted normal for age, sex, and height), but predominantly low ACT scores (≤ 19), indicating poorer asthma symptom control (Table 5).

With knowledge of FeNO levels, clinicians increased the amount of prescribed anti-inflammatory treatment in 10 of 50 subjects (20%). Of note, 50% of these subjects had FeNO values higher than 50 ppb, although 7 of 10 (70%) had FEV₁ values higher than 80% predicted and nearly half (40%) had ACT scores higher than 19, indicating good symptom control. The increases in anti-inflammatory treatment included adding or increasing the dose of ICSs (8 subjects) or adding leukotriene receptor antagonist therapy (in 2 subjects who were already on moderate to high doses of ICS therapy).

A decision analysis rooted in the peer-reviewed literature regarding the impact of FeNO on asthma-related health care usage estimated annual costs of asthma treatment for patients managed with standard of care with or without the addition of FeNO to the diagnostic armamentarium. The estimated annual cost of asthma for patients whose physicians used FeNO regardless of whether individual patient medications were decreased or increased was lower than the estimated cost of asthma without the aid of FeNO measurement (Table 6).

Table 3FeNO values by ICS use, ACT scores, and FEV₁ and asthma diagnosis

	ICS use		ACT scores		FEV ₁		Overall
	ICS ^a	No ICS	$\leq 19^b$	>19	$\leq 80\%$ Predicted	>80% Predicted	
Subjects, n (%)							
FeNO categories							
Low <25 ppb	18 (62.1)	11 (52.4)	17 (58.6)	12 (57.1)	9 (52.9)	20 (60.6)	29 (58)
Intermediate ≥ 25 – ≤ 50 ppb	6 (20.7)	4 (19.0)	5 (17.2)	5 (23.8)	3 (17.6)	7 (21.2)	10 (20)
High >50 ppb	5 (17.2)	6 (28.6)	7 (24.1)	4 (19.0)	5 (29.4)	6 (18.2)	11 (22)
FeNO (ppb)							
Mean (SD)	25.7 (21.29)	46.4 (57.45)	40.3 (50.84)	26.1 (21.96)	41.1 (46.92)	30.9 (38.55)	34.4 (41.39)
Median	17.0	23.0	18.0	13.5	24.0	14.0	17.5
Range	5–79	5–202	5–202	9–79	5–202	5–201	5–202

Abbreviations: ACT, Asthma Control Test; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.^aIncludes ICS and ICS plus long-acting β agonist combinations.^bACT scores no higher than 19 are associated with less well-controlled asthma.**Table 4**

Asthma medication changes based on FeNO results

	Overall (N = 50)
Overall	
No change	32 (64%)
Added medication or increased medication dose	10 (20%)
Subtracted medication or decreased medication dose	8 (16%)
OCS	
No change	50 (100%)
Added or increased dose	0
Subtracted or decreased dose	0
ICS-LABA	
No change	46 (92%)
Added or increased dose	3 (6%)
Subtracted or decreased dose	1 (2%)
ICS	
No change	35 (70%)
Added or increased dose	8 (16%)
Subtracted or decreased dose	7 (14%)
LTRA	
No change	47 (94%)
Added or increased dose	2 (4%)
Subtracted or decreased dose	1 (2%)

Abbreviations: ICS, inhaled corticosteroid; ICS-LABA, inhaled corticosteroid plus long-acting β agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

Discussion

This single-center observational study was designed to demonstrate how knowledge of FeNO levels, when added to traditional asthma assessment tools (including spirometry, physical assessment, and symptom scores), would influence decision making in the care of patients with asthma in a specialty asthma setting. Although this was a small study, the results of this study suggest clinicians could accurately predict the level of airway inflammation in only half their patients. After measurement of FeNO, treatment decisions were altered in more than one third of patients, resulting in substantial cost savings from the discontinuation of medications that were perceived as not needed and the projected future savings in avoidance of acute exacerbations and improved asthma control.

There is evidence that low FeNO is a good predictor of asthma control^{10,20–22} and has been shown to enable the decrease or elimination of anti-inflammatory treatment without sacrificing asthma control.^{18,23} In this study, knowledge of FeNO values led to treatment decisions that decreased or eliminated anti-inflammatory treatment in 16% of subjects.

High FeNO is evidence of uncontrolled inflammation and has been shown to be associated with increased risk for asthma exacerbations and potential future deterioration, even when there is a lack of corroborating symptoms or in the presence of normal lung

Table 5

Individual subject treatment changes in response to FeNO results

Subject ID	Age (y)/sex	Estimated FeNO level	Actual FeNO (ppb)	ACT score	FEV ₁ (% predicted)	Treatment change
Treatment decreases						
01-009	39/F	low	9	14	123	Advair 50/250 µg changed to FP 44 µg
01-010	20/F	low	9	21	97	Pulmicort 180 µg discontinued
01-012	57/F	intermediate	<5	18	71	FP 220 µg to FP 100 µg
01-030	35/M	intermediate	5	14	89	FP 44 µg discontinued
01-039	57/M	intermediate	12	16	58	FP 100 µg discontinued
01-042	40/F	low	18	14	99	LTRA discontinued
01-043	31/F	intermediate	16	16	54	QVAR 80 µg discontinued
01-047	51/F	low	10	21	94	Pulmicort 180 µg discontinued
Treatment increases						
01-004	42/F	high	60	15	60	FP 44 µg changed to Symbicort 160 µg
01-006	21/M	low	36	17	90	FP 44 µg added
01-011	20/M	low	102	19	87	FP 44 µg added
01-013	39/M	intermediate	202	11	78	FP 44 µg changed to Advair 50/250 µg
01-014	57/F	low	30	22	76	FP 44 µg changed to FP 110 µg
01-016	46/F	low	28	22	107	Symbicort 80/4.5 increased from 1 puff QD to 2 puffs BID
01-023	12/F	low	55	21	89	LTRA added
01-025	46/F	low	81	19	93	FP 44 µg added
01-045	40/F	low	35	22	86	Pulmicort 180 µg increased from 1 puff QHS to 2 puffs QHS
01-048	30/F	low	28	15	109	LTRA added

Abbreviations: ACT, Asthma Control Test; BID, twice daily; F, female; FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; M, male; QD, daily; QHS, at bedtime.

function.^{24–26} In this study, knowledge of high FeNO values led to decisions in 20% of subjects to increase anti-inflammatory doses or in some subjects to add anti-inflammatory treatments to otherwise steroid-naïve subjects, many of whom had normal lung function and unremarkable symptom scores.

The use of FeNO as an adjunct to manage asthma care is evolving, and knowledge of how best to incorporate FeNO into clinical practice has important clinical and cost-saving implications. In a recently published meta-analysis by Donohue and Jain,²⁷ FeNO was shown to predict T-helper cell type 2–mediated corticosteroid-responsive airway inflammation, leading to lower asthma exacerbation rates in those patients who received FeNO-directed therapy compared with asthma exacerbation rates in patients guided by clinically based asthma management algorithms. Similar results have been observed by others.^{5,7,28} Powell et al²⁸ randomly assigned a cohort of pregnant women with asthma to FeNO-directed asthma care or asthma care directed by clinical symptoms. They reported not only significantly fewer maternal asthma exacerbations in the FeNO-directed group, but also significantly fewer neonatal hospitalizations in the FeNO-directed group. Peirsman et al⁵ observed that the number of asthma exacerbations in children over a 52-week period was essentially halved (24% vs 48%) when treatment was based on the Global Initiative for Asthma guidelines in conjunction with FeNO rather than Global Initiative for Asthma guidelines alone. Syk et al⁷ managed asthma care in a primary care setting for longer than 1 year in 187 adult subjects who were receiving ICS therapy. Half the group was randomized to FeNO-guided management

and the other half was randomized to usual care (no knowledge of FeNO levels). Asthma exacerbations rates in the FeNO-guided group were nearly half those guided by clinical assessment alone. As evidence of the benefits of FeNO-guided asthma management accrues, there is real opportunity to lower future asthma morbidity and decrease overall asthma management costs.

The limitations of this study are that, by design, it was a small, single-center, single-visit observational trial. Although these data suggest that the use of FeNO could contribute to substantial long-term savings in the cost of asthma management, clearly a larger, longitudinal study would be needed to confirm the cost effectiveness of the use of FeNO in routine asthma management. Moreover, follow-up of these patients over time would be necessary to establish that the medication changes resulted in better asthma control (in the case of high inflammation) and no loss of asthma control in cases in which anti-inflammatory treatment was decreased or eliminated. Although FeNO results need to be interpreted in conjunction with the composite clinical picture, direct knowledge of the degree of allergic inflammation provides an objective assessment of the disease process that heretofore has for all practical purposes had to be inferred from clinical findings, and that may or may not, as this study demonstrates, reflect the true underlying pathology.

In conclusion, knowledge of FeNO augments traditional clinical assessment of airway inflammation and affects medication treatment decisions in clinical practice. This in turn is likely to translate to important cost-effectiveness implications.

Table 6

Estimated annual asthma management costs (per subject)

	Maintenance medications (US\$)	Exacerbations (US\$) ^a	Scheduled physician office visits (US\$) ^b	All asthma-related care (US\$)
Standard guidelines	1,601.16	864.37	281.68	2,747.21
FeNO in addition to standard guidelines	1,376.30	410.90	331.48	2,118.38

Abbreviation: FeNO, fraction of exhaled nitric oxide.

^aIncludes direct payer costs of unscheduled physician office visits, outpatient visits, hospital emergency department visits, inpatient hospitalizations, FeNO testing, spirometry, and rescue medications.

^bIncludes level III physician office visits, FeNO testing, and spirometry.

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