
Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide

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Background: Asthma is an inflammatory disease, yet clinical tools that evaluate asthma control do not include measures of inflammation.

Objective: To determine the correlation between fractional exhaled nitric oxide (FeNO) and each of 5 asthma control evaluation tools, namely, the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT), the National Asthma Education and Prevention Program (NAEPP) goals of therapy, the Joint Task Force Practice Parameter (JTFPP) on attaining optimal asthma control, and the Global Initiative for Asthma (GINA) guidelines.

Methods: Patients 6 years or older who had asthma were clinically evaluated by an asthma specialist. Patients completed the ACT and ACQ and underwent spirometry and FeNO measurement. The physician was blinded to FeNO results until asthma control assessments were concluded. Correlations between FeNO level and each clinical evaluation tool were calculated.

Results: One hundred patients 6 to 86 years old were enrolled. No significant association was found between FeNO level and asthma control based on ACQ ($P > .99$), ACT ($P = .53$), NAEPP ($P = .53$), JTFPP ($P = .30$), or GINA ($P = .86$) criteria. Agreement was high among the NAEPP, the JTFPP, and GINA; moderate between the ACQ and the ACT; and poor to fair between the ACT or the ACQ and the other 3 tools.

Conclusions: In addition to clinical evaluation, the incorporation of FeNO measurement in evaluating asthma is likely to lead to a more optimal pharmacotherapy, guidance in adjusting the dosage of anti-inflammatory agents, and positive long-term disease outcome.

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INTRODUCTION

Airway inflammation is central to the pathogenesis of asthma and can lead to airway remodeling and irreversible impairment of lung function.¹ Asthma control guidelines stress the importance of anti-inflammatory medications, particularly inhaled corticosteroids (ICS), as first-line treatment.² In assessing asthma control, it would be prudent to include markers of airway inflammation.

Current asthma control evaluation tools are primarily clinical parameters (eg, daytime and nocturnal exacerbations, use of short-acting β_2 -agonists [SABA], and activity limitation) and spirometric measurements. Commonly used methods to evaluate asthma control include the Asthma Control Questionnaire (ACQ),³ the Asthma Control Test (ACT),⁴ the National Asthma Education and Prevention Program (NAEPP) goals of therapy,² the Joint Task Force Practice Parameter (JTFPP) on attaining optimal asthma control,⁵ and the Global Initiative for Asthma (GINA) guidelines.⁶ None of these tools includes measurement of airway inflammation (Table 1).

Inflammatory markers such as sputum eosinophils⁷ and airway hyperresponsiveness⁸ have been shown to correlate with asthma activity and severity. However, these tests are time-consuming and not amenable to routine practice. Fractional exhaled nitric oxide (FeNO) has been shown to correlate with several markers of airway inflammation, including bronchial mucosal eosinophilia,⁹ bronchoalveolar lavage eosinophilia,¹⁰ bronchial hyperresponsiveness,¹¹ sputum eosinophilia,¹¹ and blood eosinophilia.¹²

Patients with asthma adherent to high-dose corticosteroid therapy have lower FeNO values than steroid-naïve asthmatic patients.¹³ An increase in FeNO level precedes asthma exacerbations,¹⁴ and the level decreases with the use of anti-inflammatory medications in a dose-dependent manner.¹⁵ Elevation in FeNO level has been shown to occur in the absence of a significant deterioration in lung function, daytime symptoms, or increased SABA use.¹⁶ Although FeNO measurement is currently not prevalent, it is expected to increase, particularly since affordable portable devices are becoming available.¹⁷

Few studies to date have examined the correlation between asthma control evaluation tools and control of airway inflammation. We performed this study to investigate how well 5 commonly used asthma control evaluation tools (ACQ, ACT, NAEPP, JTFPP, and GINA) correlate with FeNO.

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Table 1. Domains Assessed by Common Asthma Control Tools or Guidelines

Domain	ACQ	ACT	NAEPP	JTFPP	GINA
Daytime symptoms	X	X	X	X	X
Nighttime symptoms	X	X	X	X	X
Activity limitation	X	X	X	X	X
ED visits or hospitalizations			X		
Exacerbations					X
SABA use	X	X	X	X	X
Patient self-assessment		X		X	
Physician assessment				X	
FEV ₁ , % predicted	X		X	X	X

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ED, emergency department; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma guidelines; JTFPP, Joint Task Force Practice Parameter on attaining optimal asthma control; NAEPP, National Asthma Education and Prevention Program goals of therapy; SABA, short-acting β_2 -agonist.

METHODS

Study Population

Patients (scheduled and walk-ins) who were presenting to an allergy and asthma clinic were enrolled in the study. Patients 6 years or older with specialist-diagnosed asthma were eligible for participation. Patients were excluded if they had any of the following: respiratory tract infection within the preceding 14 days, tobacco smoking during the preceding 30 days, or atopic dermatitis. Respiratory tract infections¹⁸ and atopic dermatitis¹⁹ have been shown to increase FeNO, whereas tobacco smoking decreases FeNO.²⁰ Patients were also excluded if within 1 hour of testing they had consumed nitrate-rich foods (eg, lettuce, radishes) known to increase FeNO levels.²¹ One hundred consecutive patients provided written informed consent or assent and completed the study. The study was approved by the institutional review board of the Louisiana State University Health Sciences Center in Shreveport.

Skin Testing

Atopic sensitization was determined by skin prick testing with 32 common aeroallergens extracts: house dust mite mixture, cockroach mixture, cat pelt, dog hair, molds, and pollens of trees, grasses, and weeds (Hollister-Stier Laboratories, Spokane, Washington). A Duotip-Test II device (Lincoln Diagnostics, Decatur, Illinois) was used, and the reaction was read at 15 minutes compared with a negative control diluent and a reactive positive histamine control (1 mg/mL). The test result was considered positive if the wheal diameter was at least 3 mm greater than the negative control.

FeNO Measurement

Online FeNO measurements were performed according to the American Thoracic Society and European Respiratory Society guidelines²² using a chemiluminescence stationary device (NIOX; Aerocrine AB, Solna, Sweden). Participants were tested in the seated position without a nose clip. Through a

mouthpiece, participants inhaled to total lung capacity and exhaled at a constant pressure guided by visual cues to stabilize flow rate. A dynamic flow restrictor yielded a constant flow rate of 50 mL/s. When an exhalation plateau was reached (at least 4 seconds for children and 6 seconds for adults), the measurement was stopped. Exhalations were repeated after a brief rest period until 2 acceptable measurements (± 2.5 ppb for measurements < 50 ppb and $\pm 5\%$ for measurements ≥ 50 ppb) were obtained. The mean of 2 acceptable measurements was used for analysis. Calibration gas and nitric oxide filter were replaced just before study onset, and system calibration was performed every 14 days. FeNO measurements were performed before spirometry.

Spirometry

Lung function testing was performed according to the ATS standards²³ using a CPL System spirometer (Collins Medical Inc, Braintree, Massachusetts). The best of 3 reproducible trials for forced expiratory volume in 1 second (FEV₁) was recorded and expressed as a percentage of predicted according to reference values of Knudson.

Asthma Control Evaluation

Each patient completed the ACT and ACQ. Children younger than 12 years completed the Childhood ACT²⁴ with the help of their parents. Patients 17 years and older answered the first 6 questions of the ACQ, with the seventh question answered by the office staff based on spirometric data. The mean value of the 7 responses (each ranges from 0 to 6 points) represents the ACQ total score. Patients were questioned by an asthma specialist regarding daytime and nighttime symptoms, use of SABA, activity limitations, medication use and compliance, smoking history, exacerbations, and recent asthma-related emergency department visits or hospitalizations. Patient self-evaluation of asthma control was the response to the question, "Do you feel your asthma is well-controlled?" Physician global evaluation of asthma control was based on medical history, physical examination, and objective test results (eg, spirometry, questionnaire data). The physician was blinded to the FeNO results until clinical assessments were made. The definitions used in determining asthma control according to each tool are presented in Table 2. A prior diagnosis of allergic rhinitis and atopic status were determined by medical record review and aeroallergen skin prick testing.

The FeNO levels were classified, according to the NIOX manufacturer (Aerocrine),²⁵ into normal (< 15 ppb for children [≤ 12 years] and < 20 ppb for adults), increased (15–25 ppb for children and 20–35 ppb for adults), and high (> 25 ppb for children and > 35 ppb for adults).

Outcome Measures

Our primary objective was to investigate the correlation between FeNO and each of the 5 commonly used evaluation tools: ACQ, ACT, NAEPP goals of therapy, JTFPP recommendations, and GINA guidelines. We also examined the effect of associated allergic rhinitis or prior tobacco use on FeNO correlations. Secondary outcomes included the corre-

Table 2. Study Definitions of Asthma Control According to Each Assessment Tool

Assessment tool	Definition of controlled asthma
ACQ	Mean score ≤ 1
ACT	Score ≥ 20
NAEPP ^a	SABA use ≤ 2 times per week in previous 2 weeks Nocturnal symptoms ≤ 2 times in previous month No activity limitations No recent ED visits or hospitalizations for asthma FEV ₁ $\geq 80\%$ of predicted
JTFPP ^a	SABA use ≤ 2 times per week Asthma symptoms ≤ 2 times per week No nocturnal symptoms No activity limitations Patient self-assessment that asthma is controlled Physician global assessment that asthma is controlled FEV ₁ $\geq 80\%$ of predicted
GINA ^a	SABA use ≤ 2 times per week Daytime symptoms ≤ 2 times per week No nocturnal symptoms No activity limitations No exacerbations FEV ₁ $\geq 80\%$ of predicted

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ED, emergency department; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma guidelines; JTFPP, Joint Task Force Practice Parameter on attaining optimal asthma control; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting β_2 -agonist.

^a All criteria must be met for asthma to be considered controlled.

lation between patient and physician evaluation of asthma control and FeNO, as well as the degree of agreement among the clinical tools themselves.

Statistical Analysis

Data were analyzed using SAS statistical software, version 9.13 (SAS Institute Inc, Cary, North Carolina). Spearman correlation coefficient was used to evaluate correlation of FeNO to the ACQ or ACT expressed as continuous variables. In comparing differences between FeNO and clinical assessments, the χ^2 test was used when cells had expected frequencies of more than 5, otherwise the Fisher exact test was used. The same tests were used for comparison of patient or physician evaluation with FeNO. Data on patients 2 years or younger ($n = 15$) and those older than 12 years ($n = 85$) were analyzed separately. Adjusting for age, Cochran-Mantel-Haenszel analysis revealed that age was not a significant factor for comparisons between FeNO and the 5 clinical tools. Therefore, data on all ages were combined. Receiver operating characteristic (ROC) curves were used to model the FeNO level as a function of asthma control as determined by each of the 5 clinical tools. The ROC data were used to estimate the area under the curve (AUC). Agreement among clinical tools was evaluated using the κ coefficient. In general, κ values less than 0.4 indicate weak agreement; 0.4 to

less than 0.6, moderate agreement; 0.6 to less than 0.8, good agreement; and 0.8 or higher, strong agreement. A 2-sided $P \leq .05$ was considered statistically significant.

RESULTS

Patient Demographics

One hundred patients 6 to 86 years old (15 patients ≤ 12 years) were enrolled; 65% were white and 34% were African American (Table 3). Twenty-six percent of patients were ex-smokers, with a mean (SD) smoke-free duration of 18 (13) years. A positive skin prick test result to 1 or more aeroallergens was noted in 93.7%, and allergic rhinitis was diagnosed in 59%. Most patients (81%) were taking ICS either as monotherapy or in combination with long-acting β_2 -agonists and/or leukotriene antagonists.

Correlation Between FeNO and Clinical Evaluation Tools

Asthma was considered controlled in 69% by ACQ, in 68% by ACT, in 59% by NAEPP, in 50% by JTFPP, and in 54% by GINA criteria. No significant correlation was found between FeNO level and asthma control according to ACQ, ACT, NAEPP, JTFPP, or GINA criteria (Table 4). These findings were not influenced by the presence of allergic rhinitis or by smoking history. Evaluating FeNO at various cutoff levels to diagnose uncontrolled asthma as determined by each of the clinical tools revealed an AUC of 0.55 (95% confidence interval [CI], 0.39–0.71; $P = .49$) for the ACQ, 0.51 (95% CI, 0.37–0.65; $P = .88$) for ACT, 0.53 (95% CI, 0.42–0.65; $P = .56$) for the NAEPP, 0.56 (95% CI, 0.45–

Table 3. Characteristics of Study Participants

Characteristics	Finding (N = 100)
M:F, No.	41:59
Age, mean (range), y	42 (6–86)
Ethnic origin, %	
White	65
Black	34
Hispanic	1
Smoking history, %	
Never smoked	74
Ex-smoker	26
Pack-years, mean (SD)	16.5 (15)
Smoke-free duration, mean (SD), y	18 (13)
≥1 Positive skin prick test result, No. (%)	90 (93.7) ^a
Diagnosis of allergic rhinitis, %	59
Medications, %	
ICS only	7
ICS and LABA	30
ICS, LABA, and LTA	35
ICS and LTA	9
LTA	7
Other	2
None	10

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LTA, leukotriene antagonists.

^a Four patients not tested.

Table 4. FeNO Level in 100 Patients With Controlled and Uncontrolled Asthma According to Various Clinical Assessment Tools

Tool	No. of patients	FeNO level ^a			P value
		Normal	Increased	High	
ACQ ^b					>.99
Controlled	51	24	9	18	
Uncontrolled	23	11	4	8	
ACT					.53
Controlled	68	37	11	20	
Uncontrolled	32	15	4	13	
NAEPP					.53
Controlled	59	32	10	17	
Uncontrolled	41	20	5	16	
JTFPP					.30
Controlled	50	28	9	13	
Uncontrolled	50	24	6	20	
GINA					.86
Controlled	54	28	9	17	
Uncontrolled	46	24	6	16	

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma guidelines; JTFPP, Joint Task Force Practice Parameter on attaining optimal asthma control; NAEPP, National Asthma Education and Prevention Program.

^a Normal FeNO level was 1 to 14 ppb for children (age ≤12 years) and 1 to 19 ppb for adults (age >12 years); increased FeNO level, 15 to 25 ppb for children and 20 to 35 ppb for adults; and high FeNO level, more than 25 ppb for children and more than 35 ppb for adults.

^b For the ACQ, the number of patients is 74 because the ACQ was not applicable to 26 patients younger than 17 years.

0.68; $P = .29$) for the JTFPP, and 0.51 (95% CI, 0.40–0.63; $P = .84$) for GINA. The AUC values approximating 0.5 indicate that the FeNO level had low predictive accuracy of diagnosing uncontrolled asthma as determined by each of the clinical tools.

Correlation Between FeNO and Patient Self-evaluation and Physician Global Evaluation

Ninety-percent of patients rated their asthma as well controlled, yet 46.7% of them had elevated FeNO levels (Table 5). A statistically significant relationship was found between FeNO level and physician global evaluation. Nevertheless, 38.5% of patients with controlled asthma according to blinded physician evaluation had elevated FeNO levels, and 34.3% with uncontrolled asthma had normal FeNO levels.

Agreement Among the 5 Clinical Asthma Control Evaluation Tools

Using κ coefficient analysis, agreement comparisons of the 5 clinical evaluation tools showed a high level of agreement among the NAEPP, the JTFPP, and GINA ($\kappa = 0.82$ –0.90), moderate agreement between the ACT and ACQ ($\kappa = 0.52$), and generally poor to fair agreement between the ACQ or ACT and the other 3 clinical tools ($\kappa = 0.34$ –0.45).

Table 5. FeNO Level in 100 Patients With Controlled and Uncontrolled Asthma Based on Patient Self-assessment and Physician Global Assessment

Assessment	No. of patients	FeNO level ^a			P value
		Normal	Increased	High	
Patient assessment					.53
Controlled	–90	48	14	28	
Uncontrolled	–10	4	1	5	
Physician assessment					.001
Controlled	–65	40	12	13	
Uncontrolled	–35	12	3	20	

Abbreviations: FeNO, fractional exhaled nitric oxide.

^a Normal FeNO level was 1 to 14 ppb for children (age ≤12 years) and 1 to 19 ppb for adults (age >12 years); increased FeNO level, 15 to 25 ppb for children and 20 to 35 for adults; and high level, more than 25 ppb for children and more than 35 ppb for adults. The Fisher exact test used for patient assessment and the χ^2 test for physician assessment.

DISCUSSION

This study indicates that commonly used asthma control evaluation tools do not accurately reflect the status of airway inflammation as reflected by FeNO. Use of such tools may lead to inappropriate clinical decision making and result in suboptimal short-term and long-term care.

Several studies showed that asthma control cannot be optimally evaluated by any single parameter, particularly the patient's perception.²⁶ Other parameters viewed as objective, such as asthma exacerbations and SABA use, are actually based on self-perception of symptoms. Our study revealed poor agreement between self-perception of asthma control and FeNO level.

We observed no significant correlation between FeNO and any of the 5 clinical evaluation tools. Both the ACT and ACQ were validated against clinical parameters rather than on markers of airway inflammation.^{3,4,24} With our understanding of the pathophysiology of asthma, the inclusion of airway inflammation measurement would enhance the evaluation of asthma control.

Each of the evaluated clinical evaluation tools lacks the ability to properly gauge airway inflammation as reflected by FeNO. Evaluating the data by ROC analysis confirmed that FeNO level had a low predictive accuracy of diagnosing uncontrolled asthma as determined by each of the clinical tools. It is not surprising, therefore, that defining asthma control according to the NAEPP severity guidelines has been shown to result in substantial mislabeling, with up to 25% of patients with mild-intermittent disease experiencing exacerbations.²⁷

Asthma medication adjustments based on traditional clinical end points can lead to suboptimal asthma control and inaccurate ICS dosing.²⁸ On the other hand, ICS titration according to biomarkers of inflammation results in fewer exacerbations,²⁹ improved lung function,³⁰ and reduction in subepithelial reticular layer thickness compared with guideline-based treatments alone.³⁰ These studies further support the use of inflammatory markers in assessing asthma control.

The clinical importance of FeNO monitoring is supported by several studies. FeNO has been shown to predict asthma exacerbations during or after withdrawal of ICS therapy.^{14,16,31,32} In fact, a single FeNO measurement could predict an asthma exacerbation with an 80% to 90% positive predictive value.¹⁴ FeNO can also be used to titrate ICS dosages to the lowest effective dose, thus minimizing adverse effects. To guide ICS treatment, Smith et al³³ compared a guideline-based algorithm with FeNO level using a cutoff of 15 ppb at an exhaled flow rate of 250 mL/s (which they estimated to be equivalent to 35 ppb at a flow rate of 50 mL/s). They were able to decrease the ICS maintenance dose by an average of 40% without any increase in exacerbations. Pijnenburg et al³⁴ reported that steroid dosage titration according to FeNO level and symptoms vs conventional indicators alone led to improved airway hyperresponsiveness and inflammation without higher steroid dosages.

Although most studies show insignificant associations between FeNO and clinical or spirometric measurements,¹² a significant correlation has been reported.³⁵ However, close evaluation of the latter studies reveals a substantial number of patients with ongoing airway inflammation despite lacking clinical markers of poor control. Similarly, our study showed that 38% of patients with well-controlled asthma by physician global evaluation had evidence of ongoing airway inflammation, which supports previous reports of the presence of airway inflammation in the absence of symptoms³⁶ or reduced FEV₁.³⁷

A total of 34% of patients with physician-evaluated uncontrolled asthma demonstrated normal FeNO. This discrepancy might be explained, at least partly, by noninflammatory asthma triggers (eg, cold air and exercise). In such cases, although FeNO would not be expected to be elevated, its measurement is still valuable in that physicians may avoid unnecessary increases in ICS dosages. FeNO measurement may be used as complementary to, and not a replacement of, clinical evaluation tools.

The concept of asthma control evaluation as a gestalt of several components (only one of which is FeNO) is further suggested by the agreement analysis among the clinical assessments, indicating only fair agreement between the ACQ or ACT and the other clinical tools. Furthermore, despite having 4 of 5 tested domains in common (Table 1), the ACQ and ACT showed only moderate agreement with each other. The high level of agreement among the NAEPP, the JTFPP, and GINA should be expected given the similarity in definitions of controlled asthma (Table 2).

The fact that physician global evaluation is the only variable to correlate significantly with FeNO highlights the value of the physician's judgment. One possible explanation for this finding is that physician evaluation is based on not only standardized tools (eg, spirometry, ACT, ACQ, NAEPP) but also factors that could be considered as the clinical acumen. These components likely stem from longitudinal follow-up and include an understanding of the patient's baseline status, symptom tolerability, and compliance with medication.

Ongoing airway inflammation and airway hyperreactivity have been demonstrated in asthmatic patients who were considered to be in clinical remission.³⁶ Chronic inflammation

can lead to airway remodeling and irreversible obstruction, even in young adults.³⁸ FeNO can predict exacerbations and has the potential to enable the physician to alter anti-inflammatory therapy before symptoms develop. Furthermore, it can be used to titrate up ICS doses to minimize inflammation and possibly halt basement membrane thickening and airway remodeling.³⁹ Thus, FeNO can be considered a marker of both short- and long-term control.

A limitation of studies on FeNO has been the lack of standard reference values. Analysis of our FeNO data using 2 different cutoff values for normal (<15 ppb for children and <20 ppb for adults and <25 ppb for children and <35 ppb for adults) did not reveal significant correlations between FeNO and any of the 5 clinical tools (data not shown). Another potential limitation is the lack of cutoff values for interpreting the ACQ score. However, in a recent study, Juniper et al⁴⁰ concluded that the optimal cutoff point to distinguish asthma control by the ACQ is close to 1.00. Pollenosis may be associated with a rise in FeNO without an increase in symptoms.⁴¹ Most of our patients (80%) were evaluated during a period when there were negligible airborne pollen levels, and their data were not significantly different from the rest (data not shown).

In summary, asthma is a multidimensional syndrome that cannot be accurately evaluated solely by traditional clinical measures based on subjective symptoms and pulmonary function. Since airway inflammation is the key pathophysiologic process in asthma, it would be prudent to incorporate measures of inflammation in the evaluation. A multifaceted approach that takes advantage of both our improved understanding of asthma pathophysiology and advances in technology is needed. Commonly recommended clinical tools used to determine asthma control neither measure nor predict airway inflammation. Without knowledge of the extent of airway inflammation, the physician is limited in clinical decision making, especially in guiding and monitoring anti-inflammatory therapy. Current asthma guidelines should address this void.

Asthma control is a gestalt, and any tool that purports to evaluate it should reflect each of the key components of asthma care: clinical symptoms, activity limitation, pulmonary function, quality of life, and airway inflammation. FeNO measurement is a reproducible, easy-to-perform, and noninvasive surrogate marker of airway inflammation. However, as a single criterion, it may have limitations with sensitivity and/or specificity once inhaled corticosteroids are administered.⁴² It can be a valuable addition to, not a replacement of, clinical evaluation in the decision making on optimal pharmacotherapy. Its use in clinical practice would be desirable but requires training on using the device, knowledge of the various factors that influence the FeNO level, and experience in the interpretation and application of the test result.

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