



Identifying uncontrolled asthma in children with the childhood asthma control test or exhaled nitric oxide measurement

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ABSTRACT

Background: International guidelines highlight the importance of assessing asthma control status in children with asthma, and research on practical and objective instruments for assessing asthma control is ongoing.

Objective: To determine the role of the Childhood Asthma Control Test (C-ACT) and fractional concentration of exhaled nitric oxide (FeNO) in identifying children with not well-controlled asthma.

Methods: Children 6 to 11 years of age with asthma were enrolled in the study. They completed C-ACT and underwent FeNO and spirometric measurements during the monthly clinic visits. An asthma specialist assessed asthma control according to the gold standard Global Initiative for Asthma guideline and decided the treatment of the patients.

Results: Seventy-six children with a mean (SD) age of 8.7 (1.4) years were evaluated in the first visit, whereas 64 and 51 children were admitted for second and third visits, respectively. A C-ACT score of 22 or less had 69% sensitivity and 77% specificity in determining not well-controlled asthma, whereas an FeNO value of 19 ppb or higher had 61% sensitivity and 59% specificity in patients who completed 3 visits. Receiver operating characteristic curve analysis revealed that the C-ACT was better than FeNO for identifying patients with not well-controlled asthma (area under the curve, 0.79; $P < .001$ [C-ACT] vs .58, $P = .10$ [FeNO]). Results of multivariate generalized estimating equation analysis revealed that a C-ACT score of 22 or less (odds ratio, 8.75; 95% confidence interval, 4.35–17.59; $P < .001$) and an FeNO of 19 ppb or greater (odds ratio, 2.60; 95% confidence interval, 1.07–6.29; $P = .03$) were significant indicators for the presence of not well-controlled asthma.

Conclusion: The C-ACT is superior to FeNO in determining the control status of children with asthma and may be used as a complementary tool in clinical practice to detect children with not well-controlled asthma.

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Introduction

Updated versions of international asthma guidelines, such as the Global Initiative for Asthma¹ (GINA) and the National Asthma Education and Prevention Program,² highlight the importance of determining the disease control level to modify asthma therapy. Along with clinical manifestations, control level is ideally evaluated based on the presence or absence of applicable biomarkers for inflammation because asthma is an inflammatory disease. However, monitoring underlying inflammation tends not to be possible and/or feasible for most medical centers worldwide. Therefore, expert guidelines emphasize the control of clinical symptoms and

lung function abnormalities as more realistic and practical targets for physicians treating patients with asthma.

Research on practical and objective instruments for monitoring underlying inflammation is ongoing, and measuring the fractional concentration of exhaled nitric oxide (FeNO) has been proposed as a noninvasive, simple, and reproducible test for this purpose.^{3–6} However, several adult and childhood studies^{7–10} on tailoring asthma treatment according to FeNO levels produced conflicting results, rendering the role of FeNO in asthma control uncertain.

Instead of using inflammatory biomarkers, there is also an effort to identify novel tools that can be used easily in daily practice. The validated Childhood Asthma Control Test (C-ACT), a self-administered test consisting of 7 questions, is an easy-to-use and valuable tool for determining the disease control levels of children with asthma.¹¹ The aim of this study is to evaluate the diagnostic value of FeNO and C-ACT in identifying children with poorly controlled (either partly controlled or uncontrolled) asthma according to gold standard guideline definitions.

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Methods

Study population

Children 6 to 11 years of age who were previously diagnosed as having bronchial asthma according to the GINA guidelines¹ and presented at the Pediatric Allergy and Asthma Unit of Hacettepe University Hospital, Ankara, Turkey, between September 2009 and June 2010 were invited to participate in the study. Children who were able to undergo proper spirometric evaluation and FeNO measurements according to the guidelines¹² were included in the study. All children included in this study were followed up by our outpatient clinic for at least 1 year and were provided regular treatment according to the GINA guidelines. Patients with recent exacerbation at the time of enrollment, additional or coexisting chronic lung diseases (eg, bronchiectasis), and/or other chronic diseases were excluded. All patients and parents signed consent forms, and the study was approved by the institutional review board of Hacettepe University.

Study design

After informed consent was obtained, baseline characteristics, including aeroallergen sensitization and patient medications, were recorded for each patient. Children and parents completed the C-ACT and underwent FeNO measurement and spirometry. An asthma specialist, masked to patient C-ACT scores and FeNO results, determined disease severity and the asthma control status of each patient according to GINA control criteria and prescribed corresponding asthma treatments to best achieve or maintain a “controlled” status.

Patients returned for 3 consecutive monthly follow-up visits. Study evaluations consisted of a standardized specialist assessment, including symptom history, physical examination, and administration of C-ACT, FeNO, and lung function measurements at each visit.

Assessment of asthma control

The control status of each child was assessed according to the GINA guidelines by an asthma specialist, who was masked to C-ACT scores and FeNO values. Initially, physicians grouped patients as having well-controlled, partly controlled, or uncontrolled asthma. Patients with partly controlled and uncontrolled asthma were then classified as having not well-controlled asthma.

C-ACT survey

The official Turkish version of the C-ACT questionnaire was administered.¹³ Children and parents answered their respective parts of the test separately, and the sum of their scores was used for analysis. Absolute values for the C-ACT scores are demonstrated, and changes in C-ACT scores are expressed as a percentage of the initial value.

FeNO measurement

FeNO was measured online by the single-breath technique using a portable analyzer (NIOX-MINO; Aerocrine, Stockholm, Sweden) per the guidelines¹² and expressed as parts per billion.¹⁴ After inhalation of nitric oxide–free air to total lung capacity, the child exhaled at a constant flow rate of 50 mL/s. The mean value of 3 consecutive measurements was used for analysis. FeNO measurement was performed before pulmonary function testing. Absolute FeNO values are expressed in parts per billion, and changes in FeNO are expressed as a percentage of the initial value.

Spirometry

All patients underwent a spirometry test using the ZAN100 spirometry system (nSpire Health, Longmont, Colorado) to mea-

sure the prebronchodilator forced expiratory volume in 1 second (FEV₁), the FEV₁ to forced vital capacity (FVC) ratio, and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25%–75%}). Results were compared with references and reported as a percentage of the predicted value.¹⁵

Statistical analysis

Results were expressed as median and interquartile range, mean and standard deviation, or proportions. Statistical comparisons among the C-ACT scores, FeNO values, and spirometric variables were performed using the Mann-Whitney test. Associations among the continuous variables (C-ACT, FeNO, FEV₁, FEV₁:FVC, and FEF_{25%–75%}) were evaluated by the Pearson and Spearman correlation coefficients. $P < .05$ was considered statistically significant. A logistic regression model, using generalized estimating equations to account for repeated measurements on a subject, was used to determine independent factors for identifying not well-controlled asthma, adjusting for covariates (age, sex, and asthma treatment).¹⁶ The accuracy of C-ACT and FeNO in detecting not well-controlled asthma was determined by receiver operating characteristic (ROC) curve analysis. Areas under the ROC curves (AUC) with 95% confidence intervals (CIs) and their differences from 0.5 were calculated. For each selected cutoff point that significantly differentiated between patients with well-controlled and not well-controlled asthma, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. The GINA-defined asthma control status was used as the gold standard for all comparisons. Analyses were performed using SPSS statistical software, version 15.0 (SPSS Inc, Chicago, Illinois).

Results

Seventy-six children with a mean age of 8.7 years (range, 6–11 years) were evaluated during the first visit, whereas 64 children were admitted for a second visit and 51 children for a third visit. Patient demographic characteristics are summarized in Table 1.

Table 1
Descriptive characteristics of the study patients at the first visit^a

Characteristic	No. (%) of patients (n = 76)
Age, mean (SD), y	8.7 (1.4)
Male	47 (61.8)
Aeroallergen sensitization	41 (53.9)
Asthma therapy	
As needed salbutamol	30 (39.5)
ICS use	44 (57.9)
ICS monotherapy	36 (47.4)
ICS and LABA	4 (5.3)
ICS and LTRA	3 (3.9)
ICS, LABA, and LTRA	1 (1.3)
LTRA monotherapy	2 (2.6)
Asthma severity	
Intermittent	30 (39.5)
Mild persistent	23 (30.3)
Moderate persistent	18 (23.7)
Severe persistent	5 (6.6)
Asthma control status	
Well controlled	40 (52.6)
Not well controlled	36 (47.4)
C-ACT, median (IQR)	21.5 (19.0–24.0)
FeNO, median (IQR), ppb	17.0 (13.0–27.75)
Spirometric parameters, median (IQR)	
FEV ₁ , %	93.0 (82.0–101.75)
FEV ₁ :FVC ratio	88.5 (82.0–94.0)
FEF _{25%–75%} , %	85.0 (64.25–113.0)

Abbreviations: C-ACT, Childhood Asthma Control Test; FEF_{25%–75%}, forced expiratory flow between 25% and 75% of vital capacity; FeNO, fractional concentration of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β -agonist; LTRA, leukotriene receptor agonist.

^aData are presented as number (percentage) of patients unless otherwise indicated.

Table 2Comparison of C-ACT, FeNO, and spirometric findings of patients according to control status at each visit^a

	Visit 1 (n = 76)			Visit 2 (n = 64)			Visit 3 (n = 51)		
	WC (n = 40)	NWC (n = 36)	P value	WC (n = 45)	NWC (n = 19)	P value	WC (n = 39)	NWC (n = 12)	P value
C-ACT	24 (21–26)	19 (17–21)	<.001	25 (23–26)	20 (16–23)	<.001	24 (22–26)	23 (21–25)	.31
FeNO, ppb	16 (13–22)	20 (13–28)	.38	18 (12–26.5)	23 (16–31)	.11	16 (13–26)	21.5 (14–69)	.17
FEV ₁ , %	96 (89–103)	84 (75–94)	<.001	97 (89–102)	84 (74–94)	.001	93 (86–105)	78 (76–85)	<.001
FEV ₁ : FVC ratio	90 (84–94)	85 (80–94)	.11	91 (85–95)	87 (80–94)	.07	89 (83–94)	83 (78–86)	.02
FEF _{25%–75%} , %	94 (72–117)	66 (56–108)	.01	94 (74–121)	68 (50–99)	.01	87 (73–108)	62 (57–67)	<.001

Abbreviations: C-ACT, Childhood Asthma Control Test; FEF_{25%–75%}, forced expiratory flow between 25% and 75% of vital capacity; FeNO, fractional concentration of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NWC, not well controlled; WC, well controlled.

^aData are presented as median (interquartile range).

The percentage of children with well-controlled asthma increased at each consecutive visit (53%, 70%, and 77%). The C-ACT scores were significantly higher for patients with well-controlled asthma compared with not well-controlled asthma at the first (24 vs 19; $P < .001$) and second (25 vs 20; $P < .001$) visits, whereas scores for the 2 groups were more comparable at the third visit (24 vs 23; $P = .31$). FeNO values were lower for the well-controlled group compared with the not well-controlled group at the first (16 vs 20 ppb; $P = .38$), second (18 vs 23 ppb; $P = .12$), and third visits (16 vs 21.5 ppb; $P = .17$). However, no significant differences were found. Forty-five percent of the patients had FeNO values greater than 19 ppb at the first visit, 52% at the second visit, and 43% at the third visit. As expected, spirometric parameters were significantly higher for the well-controlled group compared with the not-well controlled group at each visit (Table 2). None of the patients required hospitalization during the study period, and only 1 patient had an unscheduled visit due to a virus, which caused mild exacerbation.

Analysis using ROC curves consistently identified scores of 22 or less for C-ACT and 19 ppb or higher for FeNO as the best cutoff points, with the highest combined sensitivity and specificity, at each consecutive visit. A C-ACT score of 22 or less had 69% sensitivity and 77% specificity in determining not well-controlled asthma, whereas an FeNO value of 19 ppb or higher had a 61% sensitivity and 59% specificity for patients who completed 3 visits (Table 3 and Table 4). The ROC curve analysis revealed that C-ACT was better than FeNO at identifying patients with not well-controlled asthma (AUC=0.79, $P < .001$, vs AUC=0.58, $P = .10$).

Sixty-four patients of the 76 total were seen at least twice, representing 115 pairs of successive visits. Loss of asthma control (well controlled in the previous visit and not well controlled in the following visit) was observed at the consequent visit on 32 occasions. When analyzed using ROC curves, a decrease greater than 15% in a patient's C-ACT score (compared with the previous visit) was found to predict not well-controlled asthma status. Our analysis with FeNO did not reveal a cutoff value for predicting loss of control status.

Table 3

Diagnostic values of the findings for C-ACT to predict not well-controlled asthma

C-ACT score	Sensitivity, %	Specificity, %	PPV, %	NPV, %
≤15	13	100	100	69
≤16	18	98	82	70
≤17	22	98	85	71
≤18	31	97	84	74
≤19	43	96	85	77
≤20	51	91	74	79
≤21	63	82	64	82
≤22	69	77	59	83
≤23	80	61	51	86
≤24	82	47	44	84
≤25	94	30	40	91

Abbreviations: C-ACT, Childhood Asthma Control Test; NPV, negative predictive value; PPV, positive predictive value.

Results of multivariate generalized estimating equation analysis revealed that a C-ACT score of 22 or lower (OR, 8.75; 95% CI, 4.35–17.59; $P < .001$) and an FeNO value of 19 ppb or higher (OR, 2.60; 95% CI, 1.07–6.29; $P = .03$) were significant indicators for the presence of not well-controlled asthma.

FeNO measurement (using a cutoff value of 19 ppb) correctly identified the disease control status in 59.5% of children who completed 3 visits (Table 5). No statistically significant differences were seen regarding age, sex, atopy, inhaled corticosteroid (ICS) use, or control status between patients for whom FeNO measurement was successful or unsuccessful in identifying the control status. However, the FeNO values of the children for whom FeNO measurement did not correctly identify the control status were significantly higher (21.0 ppb [interquartile range, 14.0–35.3 ppb] vs 15.0 ppb [interquartile range, 12.0–22.0 ppb]; $P = .003$).

We also intended to establish the potential role of C-ACT and/or FeNO measurement in predicting exacerbations and loss of asthma control in the future. However, no association was found between either the C-ACT score or the FeNO value and the patient's future asthma control status. No statistically significant correlations were found among FeNO, C-ACT scores, and lung function parameters.

Discussion

In the present study, children with well-controlled asthma had significantly higher C-ACT scores. C-ACT also emerged as a better variable than FeNO for identifying children with not well-controlled asthma. An optimal C-ACT score cutoff point of 22 was found to differentiate children with well-controlled and not well-controlled asthma. Our data also indicate that a C-ACT score decrease of greater than 15% may indicate loss of asthma control. However, the performance of FeNO in discriminating among patients with different control statuses was poor in comparison.

International guidelines recommend that asthma treatment be modified according to each child's control status.^{1,2} Patients with poorly controlled asthma may be overlooked, particularly by physicians in primary health care settings or crowded secondary and tertiary outpatient clinics. We participated in efforts to find a practical and easy-to-use tool for managing children with asthma, and using the gold standard guideline parameters, we aimed to evaluate the role of C-ACT scores and FeNO measurements in determining optimal follow-up care for children with asthma.

Table 4

Diagnostic values of the findings for FeNO to predict not well-controlled asthma

FeNO value	Sensitivity, %	Specificity, %	PPV, %	NPV, %
≥17	67	50	40	75
≥18	63	56	42	75
≥19	61	59	43	75
≥20	53	64	42	73
≥21	45	71	43	72

Abbreviations: FeNO, fractional concentration of exhaled nitric oxide; NPV, negative predictive value; PPV, positive predictive value.

Table 5
Comparison of children according to the performance of FeNO in identifying control status of patients

Characteristic	Successful	Unsuccessful	P value
Patients, %	59.5	40.5	
Age, mean (SD), y	8.8 (1.3)	8.8 (1.3)	.68
Male, %	61.5	74.2	.10
FeNO, median (IQR), ppb	15.0 (12.0–22.0)	21.0 (14.0–35.3)	.003
C-ACT, median (IQR)	23.0 (21.0–25.0)	23.0 (21.0–26.0)	.87
Aeroallergen sensitization, %	56.0	62.9	.29
ICS use, %	61.5	53.2	.31
Control status, %			
Well controlled	65.9	67.7	.82
Not well controlled	34.1	32.3	

Abbreviations: C-ACT, Childhood Asthma Control Test; FeNO, fractional concentration of exhaled nitric oxide; ICS, inhaled corticosteroid; IQR, interquartile range.

^aData are presented as percentage of patients unless otherwise indicated.

The C-ACT is a 7-question test used to assess asthma control and designed to classify children with different control statuses. Higher scores indicate better asthma control, and a score of 19 or less has been designated to classify children with poorly controlled asthma.¹¹ Recently, a second cutoff level of 12 or less was proposed to determine, with high specificity, children with “very poorly controlled” asthma who are at risk for severe exacerbations.¹⁷ In our study, C-ACT scores were significantly lower for children with not well-controlled asthma at all visits. However, we determined that a cutoff point of 22 (not 19) detected patients with not well-controlled asthma with 69% sensitivity and 77% specificity. Chen et al¹⁸ determined that a cutoff value of 20 for the Chinese population had 67% sensitivity and 77% specificity. Leung et al¹⁹ found that a cutoff value of 24 had 69% sensitivity and 63% specificity for detecting uncontrolled asthma in Chinese children and speculated that the structure of the C-ACT, which was originally developed for white children, might be responsible for the difference in cutoff scores. However, our study population also consisted of white children, so this explanation does not seem valid for our study. Along with translational issues, cultural, social, and ethnic variations and differences in physician practices when assessing patient control status per the GINA guidelines may be responsible for this discrepancy. Furthermore, assessment of control status according to the GINA criteria is based on symptom history rather than diaries obtained through routine clinical practice, and symptoms may be underreported due to recall bias. Our findings suggest that C-ACT is an efficacious tool for identifying patients with not well-controlled asthma, and a cutoff score of 22, rather than 19, might be better for identifying, particularly Turkish, patients with not well-controlled asthma. Further studies may be useful in better establishing the optimal cutoff value.

In addition to a cutoff point, we also determined that C-ACT score decreases greater than 15% between successive visits might be used to identify patients with not well-controlled asthma with a positive predictive value of 89%. However, in contrast to the findings of an adult study performed by Michils et al,²⁰ our results failed to document the usefulness of FeNO in predicting patients with not well-controlled asthma.

FeNO measurement is promoted as a reproducible, noninvasive, and feasible method of determining the level of underlying inflammation in patients with asthma.^{6,21} The results of several studies on school-age children have reported normal FeNO levels ranging from 5 to 25 ppb and have highlighted the effects of race, age, height, and atopic status to variable degrees.^{22–24} Furthermore, FeNO levels were found to be significantly higher in children with asthma. Sivan et al²⁵ reported that an FeNO value of 19 ppb has 86% sensitivity and 89% specificity in discriminating healthy individuals and patients with asthma. In a recently published study, Sachs-Olsen et al²⁶ proposed an FeNO cutoff value of 20.4 ppb with a high

specificity (97%) but low sensitivity (41%) for current allergic asthma in children. Increasingly, the trend has been to use FeNO measurement in the management of asthma treatment. However, a recent meta-analysis, which investigated studies that modify asthma treatment for children according to FeNO levels, reported unconvincing results regarding the superiority of FeNO measurement to conventional parameters for asthma management.²⁷ Leung et al¹⁹ measured the FeNO levels of children with asthma, and no significant difference was found between children with controlled and uncontrolled asthma. In our study, although the baseline FeNO values were lower in patients with well-controlled asthma, no statistically significant differences were found between patients with well-controlled and not well-controlled asthma. When potential confounding factors, such as aeroallergen sensitization, age, and sex, were compared for the 2 patient groups, no differences were found. However, ICS use, which is widely considered to have a strong effect on FeNO levels, was significantly higher in the group with not well-controlled asthma (71% vs 52%; $P = .03$). Therefore, the FeNO levels of patients with poor control status might have been affected by anti-inflammatory treatment. Although our findings did not demonstrate any significant benefit of using FeNO measurement in the follow-up period, a cutoff value of 19 ppb had relatively low sensitivity and specificity values (such as 61% and 59%, respectively) for detecting patients with not well-controlled asthma.

FeNO measurement was successful in identifying the control status of children with lower FeNO values, independent of age, sex, atopy, ICS use, and control status. Moreover, a negative predictive value of 19 or higher (75%) was much better at determining the control status than any positive predictive value (43%). Therefore, FeNO measurement may be more reliable for patients with lower FeNO values and may encourage physicians to use FeNO measurement to exclude children with controlled asthma rather than to identify children with not well-controlled asthma.

The results of our study, which indicate the superiority of C-ACT, are not surprising because C-ACT is designed to measure asthma control and has many of the same elements as the GINA-based definition of asthma control. On the other hand, FeNO is a measure of airway inflammation and not specifically intended for asthma control. It is generally perceived as a complementary tool in the treatment of children with asthma.¹⁰ Physicians should be aware of various factors, such as technical difficulties and administration of ICSs, that may impend the accuracy of the diagnostic performance of FeNO measurements.²⁸ We investigated whether FeNO can predict future loss of control and/or exacerbations better than C-ACT. However, our results did not find an association between either C-ACT or FeNO and asthma control status in the near future.

To our best knowledge, our study is one of the few studies comparing the performance of the C-ACT and FeNO measurement in assessing longitudinal changes in the control status of children with asthma. Leung et al¹⁹ also demonstrated the superiority of C-ACT compared with FeNO measurement and recommended physicians use C-ACT as a complementary tool for evaluating and treating children with asthma.

The main limitation of our study was the relatively small number of children who participated. Moreover, the dropout rate, the single study site, and the relatively short duration of the study were additional emerging limitations. However, it was a prospective study, and the study was performed by asthma specialists who were masked to patient FeNO and C-ACT scores when assessing the control status of each child per the gold standard GINA guidelines. Therefore, we were able to perform and document an objective comparison of the parameters.

In conclusion, compared with FeNO measurement, the C-ACT appears to be a more reliable tool for evaluating children with asthma, particularly in primary and secondary health centers.

Therefore, it may better serve physicians as a complementary tool for identifying children with not well-controlled asthma. However, further investigations, particularly a longer-term study with a larger group of children, is required before a definitive conclusion can be made.

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