



Disagreement Among Common Measures of Asthma Control in Children

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Background: Asthma is a worldwide problem. It cannot be prevented or cured, but it is possible, at least in principle, to control asthma with modern management. Control usually is assessed by history of symptoms, physical examination, and measurement of lung function. A practical problem is that these measures of control may not be in agreement. The aim of this study was to describe agreement among different measures of asthma control in children.

Methods: A prospective sequential sample of children aged 4 to 11 years with atopic asthma attending a routine follow-up evaluation were studied. Patients were assessed with the following four steps: (1) fraction of exhaled nitric oxide (FENO), (2) spirometry, (3) Childhood Asthma Control Test (cACT), and (4) conventional clinical assessment by a pediatrician. The outcome for each test was coded as controlled or uncontrolled asthma. Agreement among measures was examined by cross-tabulation and κ statistics.

Results: Eighty children were enrolled, and nine were excluded. Mean FENO in pediatrician-judged uncontrolled asthma was double that of controlled asthma (37 parts per billion vs 15 parts per billion, $P < .005$). There was disagreement among measures of control. Spirometric indices revealed some correlation, but of the unrelated comparisons, those that agreed with each other most often (69%) were clinical assessment by the pediatrician and the cACT. Worst agreement was noted for FENO and cACT (49.3%).

Conclusion: Overall, different measures to assess control of asthma showed a lack of agreement for all comparisons in this study.

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Abbreviations: cACT = Childhood Asthma Control Test; FEF_{25%–75%} = forced expiratory flow, midexpiratory phase; FENO = fraction of exhaled nitric oxide; PEFR = peak expiratory flow rate; ppb = parts per billion

Asthma is a problem throughout the world, and its prevalence appears to be increasing. Its cause is unknown; therefore, prevention is difficult. With the highly effective medications now available, it is possible, in principle, to control asthma, enabling almost every person with asthma to achieve a life free from symptoms and exacerbations with normal lung function.¹

Current national and international guidelines advise that asthma be categorized at each patient visit as uncontrolled, partially controlled, or controlled and that it be managed accordingly.² A person with controlled asthma has no ongoing symptoms in any situation and seldom needs to use reliever therapy.² Categorization of control relies heavily on patient-reported symptoms, but because people with asthma are known to frequently underestimate the severity of their condition,³ objective ways of corroborating patient history and physician assessment are sought.

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A number of objective methods to assess asthma control have been suggested in asthma guidelines. Use of standardized quality-of-life questionnaires, spirometry, and fraction of exhaled nitric oxide (FENO) are the most frequently used methods. The rationale for the FENO measurement is that because most patients are predominately atopic, the concentration of nitric oxide in exhaled air should mirror the level of asthma control; thus, FENO reflects the level of eosinophilic airway inflammation,⁴ which is considered to mediate atopic asthma.⁵

Because asthma is a heterogeneous condition with a number of phenotypic expressions, assessment of control in individual children may require asking patients and parents about ongoing symptoms and one or more objective tests to corroborate assessment of controlled or uncontrolled asthma. However, what combination of measures we should use is not clear in current guidelines, and the level of agreement among different measures is conflicting in different studies. The aim of the present study was to describe agreement among different measures of asthma control in children.

MATERIALS AND METHODS

Participants and Setting

Children with chronic asthma attending routine follow-up examinations were enrolled. Inclusion criteria were as follows: known asthma based on recurrent cough or wheezing that responds to a bronchodilator⁶ (bronchodilator responsiveness determined by at least 12% reversibility of FEV₁ after administration of an inhaled bronchodilator); aged 4 to 11 years; atopic with at least one positive skin prick test (a panel of Bermuda grass, corn pollen, five-grass mix, mold mix, cat hair epithelium, dog hair dander, house dust mite [*Dermatophagoides pterynissinus*] (ALK), with atopy manifesting as allergic rhinitis; ability to perform spirometry; and receiving therapy with inhaled corticosteroids for asthma and topical corticosteroids for allergic rhinitis. Children were excluded if they did not meet all inclusion criteria or were receiving oral corticosteroids, had significant other comorbid diseases, or could not perform all study measures.

Study sites were a public sector teaching hospital asthma clinic, which serves lower-income patients without medical insurance, and two pediatric private practices. The study was done in Gauteng province, South Africa, over 3 months during the summer rainfall season when grass pollen is the most prevalent aeroallergen. Written assent from children and consent from parents were obtained (University of Pretoria Ethics Committee approval 142-2006).

Study Sequence

Observations were made in a four-step sequence in the morning (9:00-11:00 AM).

Step 1: FENO was determined with a portable NIOX MINO (Aerocrine) device, following the manufacturer's recommended procedure. A single measurement was made in each patient. In 2006, Taylor⁷ published a table plotting levels of FENO to asthma

control outcomes. According to this publication, an FENO < 20 parts per billion (ppb) suggests adequate asthma control, whereas a value of > 35 ppb suggests poor asthma control. The range between 20 and 35 ppb is a gray zone where clinical interpretation is important. In this study, a cut point of FENO = 35 ppb was used to separate a child with well-controlled asthma (≤ 35 ppb) from a child with uncontrolled asthma (> 35 ppb). These cutoffs were advocated in a recent consensus statement.⁸

Step 2: Spirometry was done according to recommended procedure⁹ with a portable spirometer (SpiroPro+; CareFusion Corporation). Results were expressed as a percentage of the predicted Polgar reference values and 10% downward adjustment in predicted values for nonwhite children.¹⁰ For spirometry, FEV₁ $\geq 80\%$, force expiratory flow, midexpiratory phase (FEF_{25%-75%}) $\geq 60\%$, peak expiratory flow rate (PEFR) $\geq 80\%$ predicted, and FEV₁/FVC $\geq 80\%$ were regarded as controlled asthma. Spirometry was performed by a trained operator, and the equipment was calibrated daily.

Step 3: The childhood Asthma Control Test (cACT) was completed. The cACT is a standardized seven-item questionnaire about symptoms; four questions are answered by the child in relation to symptoms, and three are answered by the parent regarding symptoms in the past 4 weeks. The cACT has been validated against specialist-physician assessments and FEV₁.¹¹ A cACT score of ≤ 19 of 27 is regarded as inadequately controlled asthma.¹¹

Step 4: Clinical assessment was conducted, without knowledge of the preceding results, by one of seven pediatricians with a special interest in asthma. Routine clinic procedures were used with a formal, but not validated protocol. Questions regarding daytime, nighttime, and exercise-induced symptoms; use of reliever bronchodilator medication; and exacerbations of asthma are routinely asked before performing a physical examination. On completion, the pediatrician categorized the asthma as controlled, uncontrolled, or acute attack, in which case the patient was excluded from the study.

Outcome Measures

Guidelines recommend a three-way categorization into controlled, partially controlled, and poorly controlled asthma. But for the purposes of this study, partially and poorly controlled asthma were both classified as uncontrolled asthma.

Statistical Analysis

nQuery Advisor 7.0 (Statistical Solutions) and Stata 10 (StataCorp LP) were used for computations. The parameters of clinical assessment by the pediatrician, spirometry (FEV₁, FEF_{25%-75%}, PEFR, FEV₁/FVC), cACT score, and FENO were assessed to depict well-controlled (0) and uncontrolled asthma (1). Interparameter agreement was assessed using McNemar test for symmetry, and the κ statistic was used to determine agreement (poor agreement, ≤ 0.4 ; moderate agreement, 0.4-0.75; excellent agreement, > 0.75).¹² Logistic regression was conducted using the method described by Hosmer and Lemeshow.¹³

RESULTS

Eighty children were enrolled. Nine were subsequently excluded because three could not complete all assessment steps and six were found by the pediatrician at step 4 to have an acute attack. Seventy-one

children (mean age, 8.4 years; median age, 9 years) completed the study, of whom 46 were boys aged 4 to 11 years (median, 8 years) and 25 girls aged 4 to 11 years (median, 9 years). All children were from lower- or middle-income families, and all were able to speak English. Sixty-one percent were black African children.

Each test individually revealed controlled or uncontrolled asthma, using the cut points described in the "Materials and Methods" section. Clinical assessment by the pediatrician revealed 41 controlled patients (57.7%); cACT, 41 (57.7%); FENO, 47 (66.2%); FEV₁, 52 (73.2%); FEF_{25%-75%}, 51 (71.8%); PEFR, 40 (56.3%); and FEV₁/FVC, 62 (87.3%).

To interrogate the ability of each test of asthma control to agree with the other measures, three associations were determined. The most comprehensible way to express the relationships for the FENO:clinical assessment by the pediatrician was a box plot (Fig 1). Mean FENO in uncontrolled asthma was more than double that of controlled asthma (37 ppb vs 15 ppb, $P < .005$).

Each test was then compared with every other test in a series of 2×2 tables. The results for the proportion of agreement of these comparisons, as reflected by the κ statistic (either both controlled or both uncontrolled) is shown in Figure 2.

The κ statistic ranged from 0.00 to 0.67 (median, 0.18), where ≤ 0.4 is interpreted as poor agreement (most comparisons in this study) and 0.4 to 0.75 is defined as moderate agreement. Only the comparisons of FEV₁ and PEFR and FEF_{25%-75%} and FEV₁/FVC were moderately in agreement.

Finally, in a multivariate approach using logistic regression, all the measures of asthma control analyzed in this study were considered, and only FEV₁, cACT, and FENO were retained. To provide an equation by which the pediatrician could predict uncontrolled asthma, the latter (FEV₁, cACT, and FENO) were included in a logistic regression. The equation

from the study data to predict uncontrolled asthma was $y = -2.132 + 1.423(\text{FEV}_1) + 1.713(\text{cACT}) + 1.826(\text{FENO})$.

A specific patient's asthma will be predicted as uncontrolled when $y > -0.405$ ($P = e^y / (1 + e^y) > .4$ defines uncontrolled asthma). The latter cutoff gave the best diagnostic statistics for the prediction equation (sensitivity, 70%; specificity, 70.7%; positive predictive value, 63.6%; negative predictive value, 76%).

DISCUSSION

With respect to the aim of this study, overall agreement among testing methods to assess control of asthma was reached in 49.3% to 83.1% of assessments. Interparameter agreement using the κ statistic revealed poor (≤ 0.4) to moderate agreement (0.4-0.75) for all comparisons. Most tests were in poor agreement, and only the physiologic variables within spirometric assessment achieve moderate agreement.

When only a single measure of control is used, then 41 to 62 of the children with asthma (58%-87%) are classified as controlled. This finding may suggest that this cohort of children with asthma is not particularly well controlled; however, it is a typical finding of the degree of asthma control in similar studies.¹⁴⁻¹⁶

The apparent differences in mean values for FENO between the children with controlled and uncontrolled asthma as assessed by the pediatrician might appear to justify its value in measuring asthma control, but considerable overlap between the groups may render FENO insensitive for clinical use in individual children. The poorest agreement is between FENO and spirometry ($\kappa \leq 0.4$). The best agreement is between the spirometric indices FEF_{25%-75%} and FEV₁/FVC ($\kappa = 0.4-0.75$).

Asthma control assessment has been suggested in all asthma guidelines. All such guidelines stress the need for objective testing of control.

Since the mid-1990s, information on a disassociation between asthma symptoms and patient perceptions of these symptoms has been known. An early study revealed that a proportion of patients with asthma significantly underestimate disease severity and, thereby, may be at risk for increased mortality or morbidity.³ The cACT aims to overcome some of the problems in history taking. It is now promoted as a validated measure and widely used in clinical settings and research studies.

Previous studies revealed a lack of agreement between cACT and specialist assessment of asthma control¹¹ and a conflicting association between cACT and FENO^{16,17} and cACT and spirometry^{15,16,18} for the assessment of asthma control. However, there is

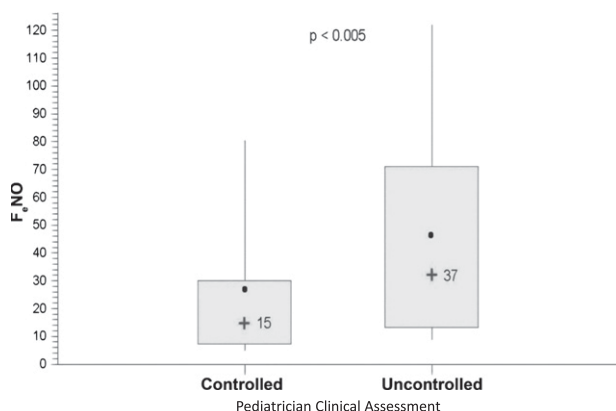


FIGURE 1. A boxplot of clinical assessment by the pediatrician. F_eNO = fraction of exhaled nitric oxide.

	cACT	F _E NO	SPIROMETRY			
			FEV ₁	FEF ₂₅₋₇₅	PEFR	<u>FEV₁</u> FVC
Clinical assessment by pediatrician	0.37	0.29	0.30	0.18	0.26	0.13
	cACT	0.00	0.24	0.18	0.03	0.00
		F _E NO	0.00	0.04	0.03	0.15
			FEV ₁	0.35	0.43	0.21
				FEF ₂₅₋₇₅	0.28	0.48
					PEFR	0.07

FIGURE 2. Proportion of observed agreement (κ statistic) among four criteria of disease control in 71 ambulatory children with asthma. Agreement is the sum of cases that are concordant for either uncontrolled or controlled asthma. cACT = Childhood Asthma Control Test; FEF₂₅₋₇₅ = forced expiratory flow, midexpiratory phase; PEFR = peak expiratory flow rate. See Figure 1 legend for expansion of other abbreviation.

evidence that cACT may be an important predictor of future asthma exacerbations or asthma risk.¹⁴ The current study supports that without additional measurements, the cACT may not uncover all children in whom asthma is uncontrolled. There is clear evidence^{19,20} that the most significantly flawed area of assessment of asthma control is that involving physician-directed assessment either by asking questions or by examination.

Previous studies revealed discrepant results for spirometric correlation with asthma symptom history and quality of life. Wildhaber et al²¹ found no significant correlation among FEV₁ ($r = -0.22$, $P = .34$), FEF_{25%-75%} ($r = -0.27$, $P = .06$), and patient symptoms. Their study, however, was limited to an analysis of only 48 children with asthma. In a larger study, Fuhlbrigge et al²² found that spirometry accurately predicts asthma symptoms and future risk of exacerbations. A potential explanation of these discrepancies relates to the actual questions used, and

careful standardization of symptom history may resolve the effect differences.

FENO measurement by means of the NIOX MINO device has been validated for successful use in children.²³ What is less obvious from the literature is what FENO measurements mean when compared with other standard measures of asthma control. There is clear evidence that FENO is correlated with airway hyper-responsiveness and steroid response in many children with asthma.²⁴ A study by Jones et al²⁵ revealed that an FENO > 15 ppb has an 88% positive predictive value of loss of asthma control, but the negative predictive value is low (25%).

Many previous studies of FENO have documented disagreement between FENO and lung function testing.^{26,27} This lack of correlation has also been revealed in the current study. Nitric oxide may not respond linearly to steroid therapy in some children, and this would need to be borne in mind if using FENO in the measurement of asthma control.²⁸

Discrepancy in objective assessments of asthma control are obvious in the literature.^{11,15-18} Although some studies find agreement among tools, others do not. In the study by Leung et al,¹⁶ there was significant agreement between various questionnaires and objective testing (spirometry). However, other studies that have attempted to compare various control assessment questionnaires (eg, Asthma Control Test, Asthma Control Questionnaire) to the end points expected in various asthma guidelines (eg, Global Initiative for Asthma, National Asthma Education and Prevention Program, Joint Task Force Practice Parameter) have failed to find a correlation. In addition, when objective assessments of inflammation (FENO) are added to the assessments, no better agreement is reached.¹⁷ Such studies find agreement when similar tools are compared (eg, between questionnaires) but not across different tool types.¹⁷ One of the problems appears to be different population groups used, different inclusion criteria, and different definitions of control for nonobjective tests. Only when studies exactly replicate study groups with identical definitions will a clear answer to control assessments become obvious. It is obvious that small differences in measurement tools can lead to large differences in effect size and prevalence estimates.

The prediction equation suggested in the current study, which uses some of the measures of asthma control, provides some value. A sensitivity and specificity of about 70% can be debated as of value. However, what future studies of asthma control require is documentation of what variables in patient assessment are missing to create an equation that perfectly predicts controlled or uncontrolled asthma in an individual person with asthma. It seems likely that included in those missing variables would need to be documentation of the asthma phenotype for a particular patient. We may, however, never achieve perfect prediction or measurement of asthma control because of the complex nature of the disease.

The study is limited by the cross-sectional design. A longitudinal study to uncover the future risk element of uncontrolled asthma would be advantageous.

CONCLUSIONS

This study revealed significant disagreement among many of the testing methods used to assess asthma control. Assessment of multiple parameters, including biomarkers, physiologic measures, symptoms, and activity limitation, would probably be necessary to categorize asthma clinical status accurately.²⁹

This study demonstrates that there is no easy answer to the measurement of asthma control. It seems likely that asthma control requires more than one end point in assessment and that both physician assessment and

objective testing are required. However, to adjudicate asthma control, very careful definition of symptoms or testing cutpoints are required.

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Dr Green: contributed to the coordination of the study; data collection; and writing, review, and approval of the manuscript.

Dr Klein: contributed to writing, review, and approval of the manuscript.

Dr Becker: contributed to the statistical analysis and review and approval of the manuscript.

Dr Halkas: contributed to the data collection and review and approval of the manuscript.

Dr Lewis: contributed to the data collection and review and approval of the manuscript.

Dr Kitchen: contributed to the data collection and review and approval of the manuscript.

Dr Moodley: contributed to the data collection and review and approval of the manuscript.

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