Disagreement between common measures of asthma control in children

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Running head: Asthma control measurements, children

Abstract

Introduction. 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 is usually 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 between different measures of asthma control in children.

Methods. Prospective sequential sample of atopic children (aged 5 –11 years) with asthma attending for routine follow-up evaluation. Patients were assessed in 4-steps: 1: Exhaled nitric oxide (F_ENO); 2: Spirometry; 3: Childhood Asthma Control Test (cACT); 4: Conventional clinical assessment by a pediatrician. Outcome for each test was coded as controlled or uncontrolled asthma. Agreement between measures was examined by cross-tabulation and kappa statistics.

Results There were 80 children enrolled and 9 were excluded. Mean F_ENO in paediatrician judged 'uncontrolled' asthma was double that of 'controlled' asthma (37ppb vs 15ppb, p<0.005). There was disagreement between measures of control. Spirometric indices revealed some correlation but of the unrelated comparisons those that agreed with one another most often (69%) were clinical assessment by the pediatrician with the cACT. Worst agreement was noted for F_ENO and cACT (49.3%).

Conclusion Overall different measures to assess control of asthma reflect lack of agreement for all comparisons in this study.

Key words: Asthma control, measurement, disagreement

Abbreviations

F_ENO – Fraction exhaled nitric oxide

ppb – parts per billion

FEV_1, - Forced expiratory volume in 1 second

$FEF_{25-75\%}$ - Forced expiratory flow over 25-75% of expiration

PEFR – Peak expiratory flow rate

FEV_1:FVC – Forced expiratory volume in 1 second / forced vital capacity

cACT – Childhood asthma control test

> - Greater than

< - Less than

$\leq$ Greater than or equal to

$\geq$ Less than or equal to

NO – Nitric oxide

ACQ – Asthma Control Questionnaire

GINA – Global Initiative for Asthma

NAEPP – National Asthma Education and Prevention Program

JTFPP - Joint Task Force Practice Parameter

Introduction

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

Current national and international guidelines advise that at each visit a patient's asthma be categorized as uncontrolled, partially controlled or controlled and that they be managed accordingly.[2] A person who has their asthma controlled is one who 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 individuals with asthma are known to frequently underestimate the severity of their condition,[3] objective ways of corroborating patient histories and physician's assessments are sought.

A number of objective methods to assess asthma control have been suggested in asthma guidelines. Use of standardized quality of life questionnaires, spirometry and exhaled nitric oxide (F_ENO) are the most frequently used methods. The rationale for F_ENO measurement being that because most patients are predominately atopic, the concentration of nitric oxide in exhaled air (F_ENO) should mirror the level of asthma control because F_ENO reflects the level of eosinophilic airway inflammation[4] which is considered to mediate atopic asthma.[5] Since asthma is a heterogenous condition with a number of phenotypic expressions, assessment of control in individual children may require questioning of 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 between different measures is conflicting in different studies.

The aim of this study was to describe agreement between different measures of asthma control in children.

Materials and Methods

Participants & Setting Children with chronic asthma attending for routine follow-up examinations were enrolled. Inclusion criteria included:

- Known child with asthma based on recurrent cough or wheezing which was bronchodilator responsive.[6] Bronchodilator responsiveness was determined by at least 12% reversibility of FEV_1 after administration of an inhaled bronchodilator;

- Aged 4-11 years old;

- Atopic with at least one positive Skin Prick Test (ALK-Abellō, Denmark) with atopy manifesting as allergic rhinitis;*

- Able to perform spirometry;

- Receiving therapy with inhaled corticosteroids for asthma and topical corticosteroids for allergic rhinitis.

* The SPT kit contained a panel of Bermuda grass, corn pollen, 5 grass mix, mould mix, cat-hair epithelium, dog-hair dander, house-dust mite (Dermatophygoides pterynissinus)

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 paediatric 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.

Study sequence Observations were made in a 4-step sequence in the morning (09h-11h).

Step 1: Exhaled Nitric Oxide Concentration (F_ENO) was determined with portable NIOX MINO® (Aerocrine AB, Sweden) following the manufacturer's recommended procedure. A single measurement was made in each patient. In 2006 Taylor published a table plotting levels of F_ENO to asthma control outcomes.[7] This publication suggested that a F_ENO value of <20 ppb suggests adequate asthma control, while a value of >35 ppb suggests poor asthma control. The range between 20 and 35 ppb is a grey-zone where clinical interpretation is important. In this study a cut-point of F_ENO 35 ppb was used to separate a child with well-controlled asthma (</=35 ppb) from a child with uncontrolled asthma (>35 ppb). These cut offs were advocated in a recent consensus statement.[8]

Step 2: Spirometry according to recommended procedure,[9] with a portable spirometer [SpiroPRO+,Viasys Healthcare GmbH, Höchberg, Germany]. Results were expressed as a percentage of the predicted value Polgar reference values

and 10% downward adjustment in predicted values for non-caucasian children.[10] For spirometry $FEV_1 \geq 80\%$, $FEF_{25-75\%} \geq 60\%$, $PEFR \geq 80\%$ of predicted and FEV_1:FVC ratio $\geq 80\%$ were regarded as controlled asthma. Spirometry was performed by a trained operator and the equipment was calibrated daily.

Step 3: Standardized Questionnaire The childhood asthma control test (cACT) was completed. cACT is a 7-item questionnaire about symptoms, 4 of which are answered by the child in relation to symptoms and 3 by the parent to reflect symptoms in the last 4 weeks. cACT has been validated against specialist physician assessments and FEV_1 (11). A cACT score $\leq$ 19/**27** is regarded as inadequately controlled asthma.[11]

Step 4: Clinical assessment was without knowledge of the preceding results by one of 7 specialist pediatricians with a special interest in asthma. Routine clinic procedures were employed with a formal, but not validated, protocol. Questions regarding daytime, night-time 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 an acute attack - in which case the patient was excluded from the study.

Outcome Measures. Guidelines recommend a 3-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 7.0 and Stata 10 (StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845 USA) was used for computations. The parameters of clinical assessment by the pediatrician, spirometry (FEV_1, $FEF_{25-75\%}$, PEFR, FEV_1:FVC), cACT score, and F_ENO were assessed to depict well controlled (0) and uncontrolled asthma (1).

Inter-parameter agreement was assessed using McNemar's test for symmetry and the kappa statistic was determined where a kappa </= 0.4 is defined as poor agreement, 0.4 – 0.75 is defined as moderate agreement and > 0.75 is defined as excellent agreement.[12]

Logistic Regression: Conducted using the method described by Hosmer and Lemeshow.[13]

Written assent from children and consent from parents was obtained. University of Pretoria Ethics Committee approval 142-2006.

Results

Eighty children were enrolled. Nine were subsequently excluded: three could not complete all assessment steps and six were found by the pediatrician at step 4 to have an acute attack. Seventy-one (mean age 8.4 years, median 9 years) completed the study of whom 46 were boys (age 5y - 11y, median 8y) and 25 were girls (age 5y - 11y, median 9y). All children were from lower or mid-income families and all were able to speak English. 61% were black African children.

Each test individually revealed controlled or uncontrolled asthma using the cut points described in the methods section. Clinical assessment by the pediatrician revealed 41 controlled (57.7%) subjects. There were 41 (57.7%) controlled subjects using the cACT, 47 (66.2%) using $F_E NO$, 52 (73.2%) using FEV_1, 51 (71.8%) using FEF_{25-75}, 40 (56.3%) using PEFR and 62 (87.3%) using FEV_1/FVC.

In order 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 $F_E NO$:clinical assessment by the pediatrician, was a box plot (Figure 1). Mean $F_E NO$ in uncontrolled asthma was more than double that of controlled asthma (37ppb vs 15ppb, p<0.005).

Each test was then compared with every other test in a series of 2x2 tables. The

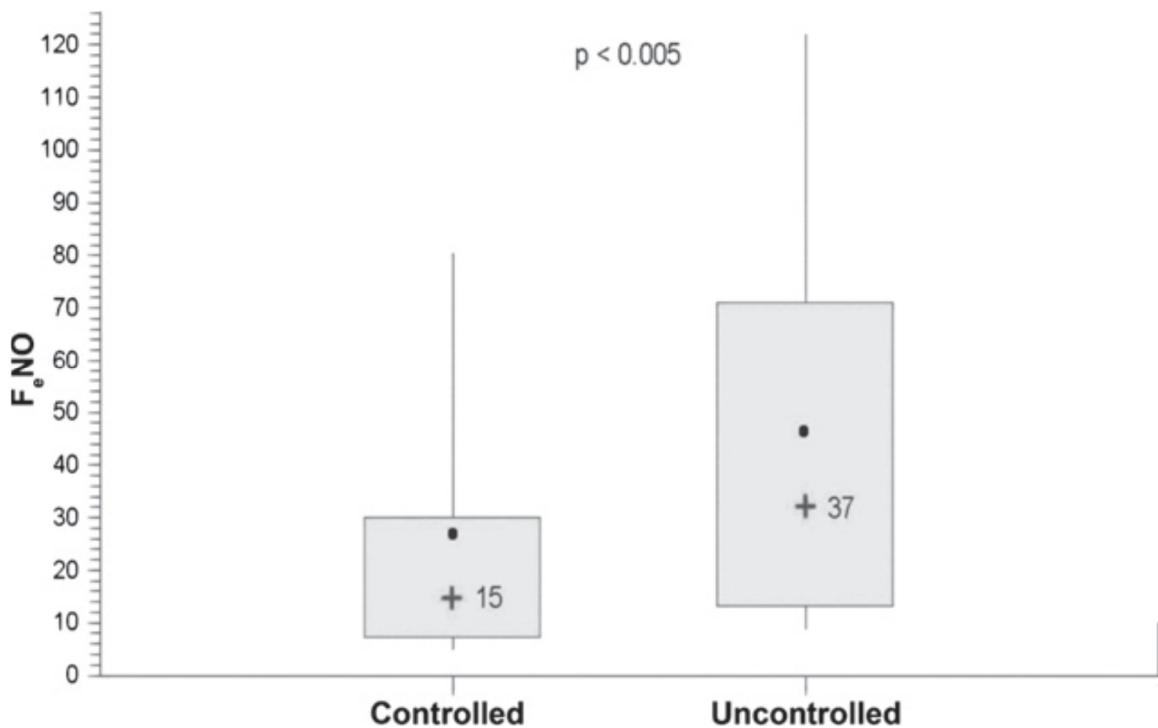results for the proportion of agreement, as reflected by the kappa statistic, of

Figure 1. A boxplot of clinical assessment by the pediatrician. F e NO 5 fraction of exhaled nitric oxide.

these comparisons (either both controlled or both uncontrolled) is reflected in

Figure 2.

Kappa, a statistical measure of agreement, ranged from 0.00 - 0.67 (median

0.18) where ≤ 0.4 is interpreted as poor agreement (most comparisons in this

study) and 0.4 – 0.75 is defined as moderate agreement   Only the comparisons

of FEV_1 and PEFR and $FEF_{25\text{-}75}$ and FEV_1/FVC are moderately in agreement.

| | cACT | F_ENO | SPIROMETRY | | | |
			FEV$_1$	FEF$_{25\text{-}75}$	PEFR	FEV$_1$ / 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_ENO			0.00	0.04	0.03	0.15
FEV$_1$				0.35	0.43	0.21
FEF$_{25\text{-}75}$					0.28	0.48
PEFR						0.07

Figure 2. Proportion of observed agreement (k 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 5 Childhood Asthma Control Test; FEF 25-75 5 forced expiratory flow, midexpiratory phase; PEFR 5 peak expiratory flow rate. See Figure 1 legend for expansion of other abbreviation.

Finally, in a multivariate approach, using logistic regression, all the measures of asthma control analyzed in this study were considered and only FEV$_1$, cACT and F_ENO were retained. In order to provide an equation by which the pediatrician could predict uncontrolled asthma, the latter (FEV$_1$, cACT and F_ENO) were included into a logistic regression. The equation from the study data to predict uncontrolled asthma was:

$$y = -2.132 + 1.423\text{FEV}_1 + 1.713\text{cACT} + 1.826F_E\text{NO}.$$

A specific patient's asthma will be predicted as uncontrolled when y > -0.405 (probability = $e^y/(1+e^y)$ > 0.4 defines uncontrolled asthma). The latter cutoff gave the best diagnostic statistics for the prediction equation, ie. sensitivity = 70%, specificity = 70.7% positive predictive value = 63.6% and negative predictive value = 76%, which reflects the ability/precision of the prediction.

Discussion

With respect to the aim of this study overall agreement, between testing methods to assess control of asthma, was reached in between 49.3 and 83.1% of assessments. Inter-parameter agreement using the kappa statistic revealed poor ($\leq$0.4) to moderate agreement (0.4 – 0.75) for all comparisons. Most tests were in poor agreement and only the physiological variables within spirometric assessment achieve moderate agreement.

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

The apparent differences in mean values for F_ENO between controlled and uncontrolled children with asthma as assessed by the pediatrician might appear to justify its value in measuring asthma control but considerable overlap between the groups renders F_ENO non-specific and insensitive for clinical use.

The poorest agreement is between F_ENO and spirometry (kappa $\leq$0.4). The best agreement is between the spirometric indices FEF_{25-75} and FEV_1/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-1990's 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 of increased mortality or morbidity.[3] The Childhood Asthma Control Test (cACT) aims to overcome some of the problems in history taking.   It is now promoted as a validated measure and is widely used in clinical settings and research studies.

Previous studies have revealed lack of agreement between cACT and specialist assessment of asthma control,[11] and conflicting association between cACT and F_ENO,[16,17] or cACT and spirometry,[15,16,18] for assessment of asthma control.

However, there is evidence that cACT may be an important predictor of future asthma exacerbations or asthma risk.[14] The current study supports the fact 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 doctor-directed assessment, either by questioning or examination.

Previous studies have revealed discrepant results for spirometric correlation with asthma symptom history or quality of life. Wildhaber et al, found no significant correlation between FEV_1 (r = -0.22 p=0.34), MEF25-75 (r=-0.27 p=0.06) and patient symptoms.[21] That study, however, was limited to analysis of only 48 children with asthma. Fuhlbrigge, in a larger study, found that spirometry accurately predicts asthma symptoms and future risk of exacerbations.[22] A potential explanation of these discrepancies relates to the actual questions used and careful standardization of symptom history may resolve the effect differences.

$F_E NO$ measurement by means of the NIOX MINO has been validated for successful use in children.[23] What is less obvious from the literature is what $F_E NO$ measurements mean when compared to standard other measures of asthma control. There is clear evidence that $F_E NO$ is correlated with AHR and

steroid response in many children with asthma.[24] A study by Jones et al has revealed that $F_ENO > 15$ ppb has an 88% positive predictive value of loss of asthma control but the negative predictive value is low (25%).[25]

Many previous studies of F_ENO have documented disagreement between F_ENO and lung function testing.[26,27] This lack of correlation has been revealed too, in the current study. Nitric oxide (NO) may, in some children, not respond linearly to steroid therapy and this would need to be borne in mind if using F_ENO in measurement of asthma control.[28]

Discrepancy in objective assessments of asthma control are obvious in the literature.[11,15-18] Whilst some studies find agreement between tools, others don't. In the study by Leung et al, there is significant agreement between various questionnaires and objective testing (spirometry).[16] However, other studies that have attempted to compare various 'control assessment questionnaires' (such as ACT and the Asthma Control Questionnaire (ACQ)) to the end-points expected in various asthma guidelines (such as GINA, National Asthma Education and Prevention Program (NAEPP) and the Joint Task Force Practice Parameter (JTFPP)) have failed to find correlation. In addition, when these authors add in objective assessments of inflammation (F_ENO) to the assessments, no better agreement is reached.[17] Such studies find agreement when similar tools are compared (for example between questionnaires) but not across different tool types.[17] One of the problems, it appears is different population groups used, different inclusion criteria, different definitions of control for non-objective tests.

Only when studies are able to exactly replicate study groups with identical definitions will a clear answer to control assessment tools 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 that has been suggested in this study, using some of the measures of asthma control, would provide some value when data obtained on a patient was 'plugged into the equation'. A sensitivity and specificity of around 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 in order 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 particular patient's asthma phenotype. We may, however, never achieve perfect prediction or measurement of asthma control because of the complex nature of the disease.

The study has the limitation of being a cross-sectional design and a longitudinal study to uncover the 'future risk' element of uncontrolled asthma would be advantageous.

Conclusion

There is significant disagreement between many of the testing methods, to assess control of asthma, in this study. 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 both doctor assessment and objective testing is required. However, in order to adjudicate asthma control, very careful definition of symptoms or testing cut-points are required.

References

1. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. Full Report 2007. National Heart, Lung and

Blood Institute. National Asthma Education and Prevention Programme. August 2007. NIH, HLBI. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

2. GINA. Global Initiative for Asthma. Global strategy for management and prevention. www.ginasthma.org.

3. Nguyen BP, Wilson SR, German DF. Patients' perceptions compared with objective ratings of asthma severity. Ann Allergy Asthma Immunol 1996;77(3):209-215.

4. Thomas PS, Gibson PG, Wang H, Shah S, Henry RL. The relationship of exhaled nitric oxide to airway inflammation and responsiveness in children. J Asthma 2005;42(4):291-295.

5. Joseph-Bowen J, de Klerk N, Holt PG, Sly PD. Relationship of asthma, atopy, and bronchial responsiveness to serum eosinophil cationic proteins in early childhood. J Allergy Clin Immunol 2004;114(5):1040-1045.

6. Motala C, Kling S, Gie R, et al. Guideline for the management of chronic asthma in children--2000 update. Allergy Society of South Africa Working Group. S Afr Med J 2000;90(5 Pt 2):524-528.

7. Taylor DR. Nitric oxide as a clinical guide for asthma management. J Allergy Clin Immunol 2006;117(2):259-262.

8. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184(5):602-15.

9. Standardized lung function testing. Official statement of the European Respiratory Society. Eur Respir J 1993 Suppl;16:1-100.

10. Quanjer PH, Borsboom GJ, Brunekreef B, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. Pediatr Pulmonol 1995;19(2):135-142.

11. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;119(4):817-25.

12. Fleiss JL. Statistical Methods for Rates and Proportions 1981, Pages 212 – 218, ISBN 0-471-06428-9.

13. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2000, Second Edition, Page 31 – 142 (Ch 2 – 4) ISBN0-471-35632-8.

14. Leung TF, Ko FW, Wong GW, Li CY, Yung E, Hui DS, Lai CK.

    Predicting changes in clinical status of young asthmatics: clinical scores or

    objective parameters? Pediatr Pulmonol 2009;44:442-9.

15. Shirai T, Furuhashi K, Suda T, Chida K. Relationship of the asthma control

    test with pulmonary function and exhaled nitric oxide. Ann Allergy Asthma

    Immunol 2008;101:608-13.

16. Leung TF, Ko FW, Sy HY, et al. Identifying uncontrolled asthma in young

    children: clinical scores or objective variables? J Asthma. 200;46(2):130-5.

17. Khalili B, Boggs PB, Shi R, Bahna SL. Discrepancy between clinical asthma

    control assessment tools and fractional exhaled nitric oxide. Ann Allergy

    Asthma Immunol 2008;101(2):124-9

18. Friedlander J, Williams A, Portnoy J, Lynch D, Sherman A, Dinakar C.

    Association of ACT and Childhood ACT Scores With FEV1 in primary and

    specialty clinics using the Asthma Control Tracker ™ Web-Based Registry. J

    Allergy Clin Immunol 2009;123:S48-S48.

19. Halterman JS, McConnochie KM, Conn KM, et al. A potential pitfall in provider assessments of the quality of asthma control. Ambul Pediatr 2003;3(2):102-105.

20. Greenblatt M, Galpin JS, Hill C, Feldman C, Green RJ. Comparison of doctor and patient assessments of asthma control. Respir Med 2009;104:356-361.

21. Wildhaber JH, Sznitman J, Harpes P, et al. Correlation of spirometry and symptom scores in childhood asthma and the usefulness of curvature assessment in expiratory flow-volume curves. Respir Care 2007;52(12):1744-1752.

22. Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. Pediatrics 2006;118:347-355.

23. Alving K, Janson C, Nordvall L. Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. Respir Res 2006;7:67.

24. Pijnenburg MW, Floor SE, Hop WC, De Jongste JC. Daily ambulatory exhaled nitric oxide measurements in asthma. Pediatr Allergy Immunol 2006;17(3):189-193.

25. Jones SL, Kittelson J, Cowan JO, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med 2001;164(5):738-743.

26. Spergel JM, Fogg MI, Bokszczanin-Knosala A. Correlation of exhaled nitric oxide, spirometry and asthma symptoms. J Asthma 2005;42(10):879-883.

27. Stirling RG, Kharitonov SA, Campbell D, et al. Increase in exhaled nitric oxide levels in patients with difficult asthma and correlation with symptoms and disease severity despite treatment with oral and inhaled corticosteroids. Thorax 1998;53(12):1030-1034.

28. Payne DN, Wilson NM, James A, Hablas H, Agrafioti C, Bush A. Evidence for different subgroups of difficult asthma in children. Thorax 2001;56(5):345-350.

29. Fuhlbrigge AL. Asthma severity and asthma control: symptoms, pulmonary function, and inflammatory markers. Curr Opin Pulm Med 2004;10(1):1-6.