

Original article

Childhood Asthma Control Test and airway inflammation evaluation in asthmatic children

Background: The Childhood Asthma Control Test (C-ACT) has been proposed as a tool in assessing the level of disease control in asthmatic children. To evaluate the position of C-ACT in the clinical management of asthmatic children, in relationship to the level of airway inflammation as assessed by fractional exhaled nitric oxide (FeNO) and with lung function.

Methods: A total of 200 asthmatic children were included in the study: 47 children with newly diagnosed asthma ('New') and without any regular controller therapy; and 153 children with previously diagnosed asthma, treated according to GINA guidelines, and evaluated during a scheduled follow-up visit ('Follow-up'). Childhood Asthma Control Test, FeNO and lung function [forced expiratory volume 1 (FEV1) and forced vital capacity (FVC)] were evaluated.

Results: In New vs Follow-up participants, C-ACT score ($P < 0.001$), FVC ($P < 0.005$) and FEV1 ($P < 0.05$) were significantly lower, and FeNO ($P = 0.011$) were significantly higher. In New, but not in Follow-up participants, significant correlations were observed between C-ACT score and FeNO ($r = -0.51$; $P < 0.001$), FEV1 ($r = 0.34$; $P = 0.022$) and FEV1/FVC ($r = 0.32$; $P = 0.03$). This lack of correlation in Follow-up visits seemed attributable to dissociation between inadequately controlled asthma by C-ACT ratings with normalization of other measures such as FeNO levels.

Conclusions: This study confirms and expands the concept that C-ACT is complementary to, but not a substitute for, other markers of disease control in asthmatic children, especially in the context of follow-up visits.

G. L. Piacentini¹, D. G. Peroni¹,
A. Bodini¹, E. Bonafiglia¹, E. Rigotti¹,
E. Baraldi², A. H. Liu³, A. L. Boner¹

¹Clinica Pediatrica Università di Verona, Verona, Italy; ²Dipartimento di Pediatria Università di Padova, Padova, Italy; ³National Jewish Medical and Research Center and the University of Colorado School of Medicine, Denver, CO, USA

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Dr Giorgio L. Piacentini
Dipartimento di Pediatria
Policlinico G.B. Rossi
37134 Verona
Italy

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The need for a reliable method to assess the level of asthma control was apparent on the basis of the recent update of international GINA guidelines (1) that suggest tailoring asthma treatment to the level of disease control rather than severity. In this latest version, the GINA guidelines indicate that, ideally, control should be applied not only to address clinical manifestations, but also to the level of airway inflammation. However, the GINA panel of experts recommended a treatment aimed at controlling the clinical features of disease, along with lung function, 'because of cost and/or general unavailability of test' able to monitor airway inflammation (1). Nevertheless, it has been reported that neither symptoms nor lung function alone adequately reflect the underlying level of airway inflammation (2–4). On the other hand, the precise role of airway inflammation in the clinical outcomes of asthma is still under debate (5–9).

The Childhood Asthma Control Test (C-ACT) was recently validated and proposed as an accurate and reliable tool, complementary to lung function testing, to assess the level of disease control in asthmatic children (10). Measures of fractional exhaled nitric oxide (FeNO) have been well correlated with eosinophilic inflammation in patients with

asthma (11–14). The development and recent U.S. FDA approval of multiple devices to measure FeNO (<http://www.fda.gov>) has improved the feasibility of measuring FeNO in clinical practice. Recently, Senna et al. (15) showed a good correlation between ACT and FeNO in a small group of adults referred to a specialist for respiratory complaints, but without a prior diagnosis of asthma.

To the best of our knowledge, no currently available publications have evaluated a potential correlation of C-ACT with validated markers of airway inflammation in asthmatic children. This study was aimed to assess the relationship of C-ACT with the level of airway inflammation as assessed by FeNO and with lung function in order to evaluate its alternative or complementary role in the management of asthma in newly diagnosed and regularly followed-up children.

Methods

Study participants

Two hundred consecutive allergic asthmatic children able to perform correct spirometric evaluation and FeNO measurements

according to guidelines (16) were included in this study and allocated in two groups:

'New': 47 children who were referred for the first time to a specialist because of respiratory symptoms suggestive of asthma and who were confirmed to be asthmatic on the basis of their symptoms, plus reversibility of forced expiratory volume 1 (FEV₁) of at least 12% after the administration of salbutamol 400 mcg metered dose inhaler (MDI) (17). None of the children in this group were receiving regular asthma treatment at the time of this visit, but 18 of them had been previously treated with short courses of β_2 agonists and inhaled corticosteroids (ICS) as prescribed by their family physicians.

'Follow-Up': 153 children who were already diagnosed as asthmatics, treated according to GINA guidelines, and returning for a scheduled follow-up visit (1). Of these patients, only 16 children with intermittent asthma (10%) were not receiving a regular treatment with controller medications, whereas the rest of the group (90%) had persistent asthma and were treated with regular ICS, either alone or in combination with long acting beta agonists or montelukast. In the three months prior to the study, the only anti-asthma medication that the 16 patients with intermittent asthma were receiving was salbutamol as needed.

The study evaluations consisted of a standardized specialist assessment, including administration of the C-ACT, spirometric lung function evaluation, and FeNO measurement.

The study design was approved by the ethical committee at the University of Verona and Padova. The study was supported by institutional University funding. Aerocrine AB, Sweden, kindly provided some NIOX MINO[®] sensors for unrestricted use which were employed at the purposes of this study.

Childhood Asthma Control Test

The officially developed Italian translation of the C-ACT questionnaire (Childhood ACT English version available at <http://www.asthmacontrol.com> – Italy/Italian final version 09 June 06 – Mapi Research Institute) was administered as a first step in the evaluation of the asthmatic children. Children and parents answered the respective section of the questionnaire independently of each other, with the specific request to the parents of younger preschool children to provide assistance limited to the reading of the questions and answers reported in their section. The physicians performing the clinical evaluations calculated the C-ACT scores and entered them into an electronic file.

Lung function and FeNO evaluation

Lung function was evaluated by a Fukuda Sangyo spirometer model ST-250 Spiroanalyzer (Fukuda Sangyo Inc., Chiba, Japan). Forced expiratory volume 1, FEV₁/forced vital capacity (FVC) and % increase in FEV₁ after the administration of 400 mcg of salbutamol were recorded.

Fractional exhaled nitric oxide levels were evaluated by a NIOX MINO[®] device (Aerocrine AB, Solna, Sweden). NIOX MINO[®] is based on electrochemical analysis and in line with the procedures published for FeNO measurement (18). It has been validated with the existing technology based on chemiluminescence with accuracy of ± 5 ppb compared to NIOX (Aerocrine AB), showing an average disagreement of 0.5 ppb with a mean SD of 3.8 ppb, and a high linearity and accuracy when compared with reference gases (18, 19). On the basis of the data provided by the manufacturer, which included sensor stability within 5 ppb or 15% throughout its lifetime, the device was 510(k) cleared (K072816) by FDA, it has been demonstrated to be repeatable (20) applicable in research and clinical practice (21) and it has

been used in a number of recent cross-sectional and longitudinal clinical studies (22–26).

Statistical analyses

Between-groups comparisons were performed by unpaired Student's *t*-test or ANOVA when more than two groups were analyzed. Relationships between the investigated parameters were assessed by a linear regression test. Tests were considered significant if $P < 0.05$. Data are expressed as mean $\pm$ SD.

Results

The mean age of the children evaluated in this study was 8.9 years (± 2.8). Childhood Asthma Control Test was well accepted by all of the children and parents who, in most cases, acknowledged that it was simple to understand and to complete. New participants were significantly worse than Follow-up participants in all measures of asthma control, including C-ACT score ($P < 0.001$), FeNO ($P = 0.011$), FVC ($P < 0.005$), FEV₁ ($P < 0.05$) and bronchodilator response ($P < 0.05$) (Table 1). Using the validated C-ACT cut-point score of 19 or less to indicate inadequate asthma control (8), 42.5% ($n = 20$) of New participants vs 13.7% ($n = 21$) Follow-up participants were inadequately controlled ($P < 0.005$). Assuming an FeNO measure of 20 ppb or more to indicate inadequate control of airways inflammation (5), 66.0% ($n = 31$) of New participants vs 40.5% ($n = 62$) Follow-up participants were inadequately controlled ($P < 0.01$).

For New participants, their C-ACT scores demonstrated good correlations with inflammatory markers: FeNO ($r = -0.51$; $P < 0.001$) and modest correlations with lung dysfunction: FEV₁% ($r = 0.34$; $P < 0.02$) and FEV₁/FVC ratio ($r = 0.32$; $P < 0.03$) (Table 2). In comparison, the C-ACT scores of Follow-up participants did not correlate with these measures of airway inflammation or dysfunction. The clinical implications of these differences in the correlation of asthma control measures between New and Follow-up participants can be appreciated in the Fig. 1 graphical representations of C-ACT score with FeNO measure. In New participants (Fig. 1A),

Table 1. Summary of results

	Newly diagnosed ($n = 53$)	Regular follow-up ($n = 147$)	<i>P</i> -value*
C-ACT score	20.0 $\pm$ 4.9†	22.7 $\pm$ 3.5	0.001
FeNO	34.3 $\pm$ 26.9	24.1 $\pm$ 22.8	0.011
FVC (%)	81.8 $\pm$ 15.6	89.0 $\pm$ 14.5	0.005
FEV ₁ (%)	85.6 $\pm$ 13.8	90.2 $\pm$ 12.8	0.05
FEV ₁ /FVC	91.5 $\pm$ 7.6	90.3 $\pm$ 8.5	n.s.
Δ FEV ₁	9.96 $\pm$ 8.87	6.15 $\pm$ 11.5	0.05

*Unpaired *t*-test.

†Mean $\pm$ SEM.

Table 2. Correlation of C-ACT scores with other investigated parameters in newly diagnosed and regularly followed-up asthmatic children

	FeNO	FEV ₁ (%)	FEV ₁ /FVC
Newly Diagnosed	$r = -0.51$; $P < 0.001$	$r = 0.34$; $P < 0.022$	$r = 0.32$; $P < 0.03$
Regular Follow-up	n.s.	n.s.	n.s.

C-ACT scores correlated with FeNO levels such that 25.5% rated as controlled and 34% were inadequately controlled by both measures. In comparison, in Follow-up participants, the lack of correlation between C-ACT score and FeNO is attributable to the near-absence of participants rating as inadequately controlled by both measures (i.e. 2.6% in bottom right quadrant Fig. 1B).

Since long acting beta-2 agonist (LABA) can influence C-ACT but not FeNO, a separate correlation analysis was performed excluding the 73 Follow-up children on LABA treatment but this failed to show any from the correlation between the above referred parameters in the remaining 80 patients.

Considering a supplementary analysis pooling new referrals, who were essentially steroid naïve, and children not receiving regular treatment with ICS, a significant negative correlation between C-ACT score and FeNO levels was still demonstrated ($n = 75$; $r = -0.335$ $P = 0.0033$).

Discussion

The main results of this study suggest that the assessment of asthma control by C-ACT questionnaire in children is significantly related to the level of FENO in newly diagnosed patients but not in those already under regular follow-up. A significant negative correlation was still observed when those children in the 'follow-up' group who were not receiving a regular treatment with ICS were pooled with the 'new' ones. In adult asthmatics, the ACT questionnaire was demonstrated to be reliable and valid in assessing asthma control both in patients under the care of asthma specialists (27) and in those coming for the first time to the attention of an expert (28). In a previous study by Rosias et al., in a smaller number of asthmatic children performing the assessment of disease control by a different questionnaire, asthma control questionnaire (ACQ) (29), it was demonstrated a relationship, though nonsignificant, with FeNO. More recently, a study by Khalili et al. failed to found a significant association between FeNO and asthma control based upon ACQ and ACT questionnaires (30) whereas Michilis and coworkers showed a significant relationship of ACQ with FeNO (31). Nevertheless, in the latter study, the ability to mirror the level of asthma control was less evident in patients using high doses of corticosteroids (31). This finding is somehow consistent with our results. In another study, on

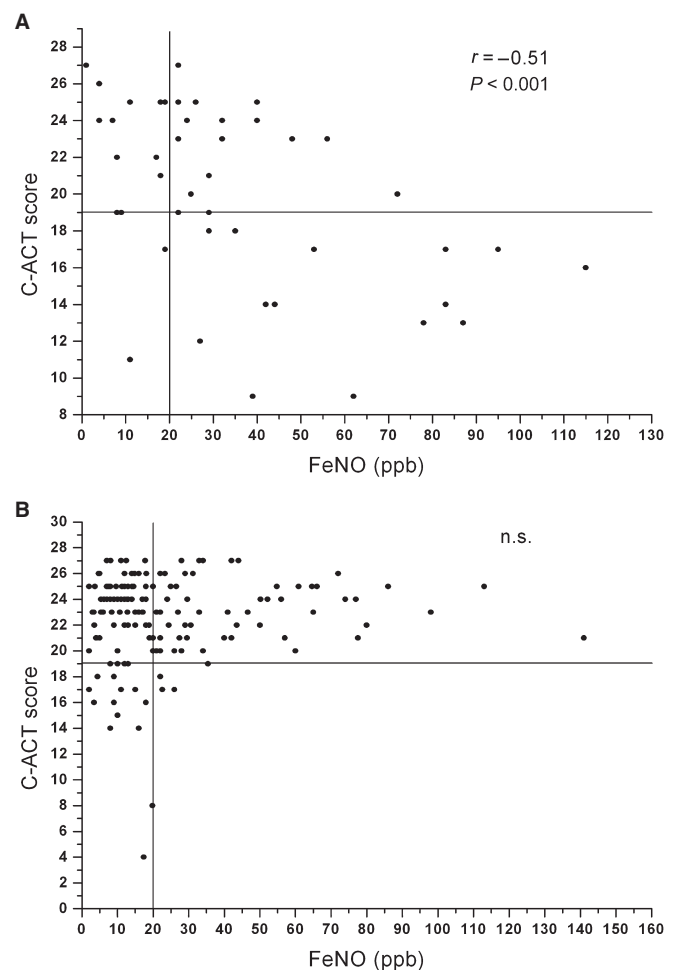


Figure 1. Relationship between C-ACT and FeNO in newly diagnosed (A) and regularly followed-up (B) asthmatic children.

a wide general population of asthmatics, only 10% of the patients presented with both an ACT < 19 and an FEV₁ $< 80\%$ of predicted (32). These data supported the explicit GINA recommendation that questionnaires addressing the level of disease control need to be considered along with the results of lung function measurement (1).

A recent paper highlighted the potential gainful application of the C-ACT in children that, in their study population, was associated with specialist clinicians' global assessment of asthma control, reported need for an increase in asthma medication, and spirometric measurement of FEV₁ (9). The present study was performed to determine if the C-ACT should be regarded as a complementary or alternative test to the assessment of airway inflammation and airflow limitation in asthmatic children seen at an asthma specialist setting. The population of the present study was distinguished into two groups: newly diagnosed asthmatic children and those returning for a follow-up visit. These two populations were similar in terms of age but the analysis of their

characteristics revealed, in children with newly diagnosed disease, lower C-ACT scores, higher levels of bronchial obstruction with greater reversibility of airflow limitation, and higher FeNO values.

In newly-diagnosed asthmatic children, there was a concordance between C-ACT < 19 and both FeNO > 20 ppb and FEV₁ < 80% predicted in 55% of cases, that further increased to 85% when the concordance of C-ACT < 19 was measured with either one or the other parameter (increased FeNO or reduced FEV₁). In contrast, in the larger group of previously diagnosed asthmatic children who returned for a follow-up visit (*n* = 153), we found a concordance of an C-ACT score < 19 with either increased FeNO value or low FEV₁ in only 33.3% of cases, and none showed a concordance among all three parameters.

Viewed differently, the large majority of Follow-up participants rated as inadequately controlled by only one of the following two parameters: 11.1% by C-ACT only, and 37.9% by FeNO only. This implies an important decision point in the algorithm for the optimal approach to asthmatic children in follow-up visits. Those who are C-ACT controlled/FeNO uncontrolled are symptomatically controlled, but have evidence of persistent inflammation and could be at risk for future asthma problems. This sub-group may include asthmatic children with poor symptom perception and in whom objective measures may be essential to accurately evaluate their control level. In comparison, those who are C-ACT uncontrolled/FeNO controlled may have adequately addressed the atopic inflammation in their airways, but continue to have symptom persistence for other reasons, including co-morbidities (e.g. sinusitis, GERD), noneosinophilic asthma (33, 34) and masquerades of asthma (35, 36). The fact that, in the Follow-up group, there were no children reporting symptoms and a raised FeNO (C-ACT uncontrolled/FeNO uncontrolled) could be partially

explained by a poor symptom-perception due to adaptation to their level of disease in a number of subjects who, therefore, will be allocated in the group of symptom controlled/FeNO uncontrolled asthmatics.

Since only a minority of follow-up children with low C-ACT scores had elevated FeNO or reduced lung function measures, it is tempting to conclude that the information captured by the C-ACT is complementary to, but not a surrogate for, the objective measures of airway disease. In other words, the C-ACT questionnaire may convey something that inflammatory markers and spirometry cannot assess.

A major difference between our two groups is that asthma treatment had not yet been regularly started in New participants, but was daily controller therapy for Follow-up participants (except for the small proportion of children with intermittent asthma).

For these reasons, it is not surprising to have found a better correlation between markers of airway inflammation, lung function and C-ACT in newly diagnosed patients who had poorer lung function, worse airway inflammation, lack of regular controller treatment, and possibly a more pronounced perception of asthma symptoms that motivated them to obtain consultation from an asthma specialist.

The cross-sectional design of this study does not allow to determine whether the C-ACT or inflammometry, or neither, can guide to baseline control or exacerbation frequency. A longitudinal study, based upon the results of the present one will allow to address this question.

In conclusion, this study suggests that the C-ACT can be utilized as part of the routine evaluation of asthmatic children, as a complement, but not as an alternative to other tools, such as spirometry and FeNO measurement. In particular, in Follow-up visits, the combination of different tools can increase the quality of patient evaluations and improve the assessment of disease control.

References

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Available at: <http://www.ginasthma.com/Guide-lineitem>.
2. Crimi E, Spanevello A, Neri M, Ind W, Rossi GA, Brusasco V. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. *Am J Respir Crit Care Med* 1998;**157**: 4-9.
3. Gibson PJ. Monitoring the patient with asthma: an evidence-based approach. *J Allergy Clin Immunol* 2000;**106**: 17-26.
4. Lundback B, Dahl R. Assessment of asthma control and its impact on optimal treatment strategy. *Allergy* 2007; **62**:611-619.
5. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;**176**:231-237.
6. Fritsch M, Uxa S, Horak F Jr, Putschoegl B, Dehlink E, Szepfalusi Z et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006;**41**:855-862.
7. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma. *N Engl J Med* 2005;**352**: 2163-2173.
8. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2005;**172**:831-836.

9. Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;**372**:1065–1072.
10. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;**119**:817–825.
11. Van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. *Am J Respir Crit Care Med* 2001;**164**:2107–2113.
12. Warke TJ, Fitch PS, Brown V, Taylor R, Lyons JD, Ennis M et al. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax* 2002;**57**:383–387.
13. Lex C, Ferreira F, Zacharasiewicz A, Nicholson AG, Haslam PL, Wilson NM et al. Airway eosinophilia in children with severe asthma: predictive values of noninvasive tests. *Am J Respir Crit Care Med* 2006;**174**:1286–1291.
14. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;**35**:1175–1179.
15. Senna G, Passalacqua G, Schiappoli M, Lombardi C, Wilcock L. Correlation among FEV1, nitric oxide and asthma control test in newly diagnosed asthma. *Allergy* 2007;**62**:207–212.
16. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;**171**:912–930.
17. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;**161**:309–329.
18. Menzies D, Nair A, Lipworth BJ. Portable exhaled nitric oxide measurement: comparison with the "gold standard" technique. *Chest* 2007;**131**:410–414.
19. Hemmingsson T, Linnarsson D, Gambert R. Novel hand-held device for exhaled nitric oxide-analysis in research and clinical applications. *J Clin Monit Comput* 2004;**18**:379–387.
20. Takalo R, Piirilä P, Sovijärvi AR. Repeatability of successive measurements with a portable nitric oxide analyser in patients with suggested or diagnosed asthma. *Scand J Clin Lab Invest* 2008;**68**:830–832.
21. Boot JD, de Ridder L, de Kam ML, Calderon C, Mascelli MA, Diamant Z. Comparison of exhaled nitric oxide measurements between NIOX MINO electrochemical and Ecomedics chemiluminescence analyzer. *Respir Med* 2008;**102**:1667–1671.
22. Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. *Allergy* 2009 (Epub ahead of print).
23. Torre O, Olivieri D, Barnes PJ, Kharitonov SA. Feasibility and interpretation of FE(NO) measurements in asthma patients in general practice. *Respir Med* 2008;**102**:1417–1424.
24. Bodini A, Peroni D, Loiacono A, Costella S, Pigozzi R, Baraldi E et al. Exhaled nitric oxide daily evaluation is effective in monitoring exposure to relevant allergens in asthmatic children. *Chest* 2007;**132**:1520–1525.
25. Vahlkvist S, Sinding M, Skamstrup K, Bisgaard H. Daily home measurements of exhaled nitric oxide in asthmatic children during natural birch pollen exposure. *J Allergy Clin Immunol* 2006;**117**:1272–1276.
26. de Jongste JC, Carraro S, Hop WC, CHARISM Study Group, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009;**179**:93–97.
27. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P et al. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;**113**:59–65.
28. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA et al. Asthma Control Test: Reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;**117**:549–556.
29. Rosias PRP, Dompeling E, Dentener MA, Pennings HJ, Hendriks HJE, Van Iersel MPA et al. Childhood asthma: exhaled markers of airway inflammation, asthma control score and lung function test. *Ped Pulmonol* 2004;**38**:107–114.
30. 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**:124–129.
31. Michilis A, Baldassare S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. *Eur Respir J* 2008;**31**:539–546.
32. Lenoir M, Williamson A, Stanford RH, Stempel DA. Assessment of asthma control in a general population of asthmatics. *Curr Med Res Opin* 2006;**22**:17–22.
33. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;**61**:817–827.
34. Taylor DR, Bush A. Clinical use of exhaled nitric oxide measurements. *Lancet* 2009;**373**:382.
35. Weinberg M, Abu-Hasan M. Pseudo-asthma: when cough wheezing and dyspnea are not asthma. *Pediatrics* 2007;**120**:855–864.
36. Peroni D, Piacentini G, Bodini A, Boner AL. Childhood Asthma Control Test in asthmatic children with dysfunctional breathing. *J Allergy Clin Immunol* 2008;**121**:2667.