

CONTROL

Association of Asthma Education with Asthma Control Evaluated by Asthma Control Test, FEV₁, and Fractional Exhaled Nitric Oxide

JUNPEI SAITO, M.D., PH.D.,* SUGURU SATO, M.D., PH.D., ATSURO FUKUHARA, M.D.,
YASUKO SATO, M.T., TAKEFUMI NIKAIIDO, M.D., YAYOI INOKOSHI, M.D., NAOKO FUKUHARA, M.D.,
KAZUE SAITO, M.D., TAEKO ISHII, M.D., YOSHINORI TANINO, M.D., PH.D., TAKASHI ISHIDA, M.D., PH.D.,
AND MITSURU MUNAKATA, M.D., PH.D.

Department of Pulmonary Medicine, School of Medicine, Fukushima Medical University, Fukushima, Japan.

Background. Asthma education is an important adjunct for asthma control although the way asthma education affects asthma outcomes is poorly understood. The asthma control test (ACT), forced expiratory volume in 1 s (FEV₁), and fractional exhaled nitric oxide (FeNO) have all been used as markers of asthma control. However, the use of FeNO as a surrogate marker remains controversial. **Objectives.** (i) To examine whether asthma education is associated with asthma control; (ii) to compare absolute levels and changes of ACT, FEV₁, and FeNO over a year; and (iii) to evaluate whether FeNO can be used as an additional marker of asthma control. **Methods.** Fifty asthmatics with poor adherence (12 mild, 21 moderate, and 17 severe) received asthma education at study entry. Medications were unchanged for the first 3 months, and ACT, FEV₁, and FeNO measurements were recorded at entry, 3, 6, and 12 months. Asthma control was assessed at each visit and patients were categorized as either “stable” or “unstable” asthmatics according to the global initiative for asthma (GINA) guidelines. **Results.** A significant decrease in FeNO and increase in ACT score were noted in the stable asthmatic group at 3 months ($p < .001$), and this persisted over 12 months. Significant correlations were seen between changes (Δ) in FeNO, ACT, and FEV₁ over time. However, significant correlations between the absolute levels were not maintained over 12 months. A decrease of $\geq 18.6\%$ in FeNO and a ≥ 3 -point increase in ACT score (sensitivity: 80% and 73.3% and specificity: 83.3% and 87.5%, respectively) were associated with stable asthma control although the absolute levels were not. **Conclusions.** Asthma education may be useful to achieve stable control. In addition, changes rather than absolute levels of FeNO and ACT may be better markers of asthma control.

Keywords asthma control, asthma control test questionnaire, asthma education, fractional exhaled nitric oxide

INTRODUCTION

Interventions that aim to enhance medication adherence have recently been developed (1), although studies of adults and children with asthma show that approximately 30%–50% of those on asthma therapy are nonadherent to therapy at least for part of the time (2–4). Therefore, educating patients on how to manage their asthma more effectively should be used to improve patients’ knowledge and influence their decision-making process regarding disease management, resulting in greater treatment adherence. However, the way asthma education affects asthma control remains poorly understood.

Asthma symptom questionnaires, spirometry, sputum eosinophil cell counts, and airway hyperresponsiveness (AHR) are potential ways of monitoring asthma control. Of these, the global initiative for asthma (GINA) guidelines recommend asthma symptom questionnaires and spirometry as conventional approaches for managing asthma. These are easy to perform and are considered to be an indirect marker of underlying airway inflammation (5). However, directly monitoring airway inflammation may be a better and more reliable method. Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible, and noninvasive marker for directly detecting allergic airway inflammation

(6–9). However, the use of FeNO as a surrogate marker of asthma control remains controversial (6, 10).

The aims of this study were to examine whether an intensive asthma educational program is associated with asthma control, to compare changes of predictive markers for asthma control [asthma control test questionnaire (ACT), forced expiratory volume in 1 s (FEV₁), and FeNO] over a 12-month period following asthma education and finally to evaluate whether FeNO measurements could be used as an additional marker of asthma control compared with ACT and FEV₁.

METHODS

Subjects

Asthmatic patients with persistent disease and poor adherence were recruited. All subjects had attended the outpatient clinic at the Department of Pulmonary Medicine, Fukushima Medical University Hospital for more than 6 months. Asthma was diagnosed according to a clinical history of characteristic symptoms (i.e., dry cough, wheezing, chest tightness, and breathlessness) and the presence of either bronchial hyperresponsiveness to methacholine or bronchodilator reversibility $\geq 12\%$ (5). Subjects were excluded if they were current smokers, had other respiratory diseases, or had a respiratory tract infection within 6 weeks of study entry. Poor adherence was defined as the

*Corresponding author: Junpei Saito, M.D., Ph.D., Department of Pulmonary Medicine, School of Medicine, Fukushima Medical University, Hikarigaoka-1, Fukushima 960-1295, Japan; Tel: +81-24-547-1360; Fax: +81-24-548-9366; E-mail: junpei@fmu.ac.jp

presence of at least one of the following in the previous 6 months: (i) failure to follow treatment by missing any prescribed asthma medications more than 1–2 times per week; (ii) a missed follow-up appointment for more than 4 weeks without taking appropriate medications; (iii) difficulty in using prescribed inhalers evaluated by observing and assessing the patient's demonstration of a sample inhaler device, and (iv) the requirement of high-dose inhaled corticosteroid (ICS) due to uncontrolled symptoms. Adherence to therapy and current medications was assessed by respiratory consultants in our department following a patient interview, review of medical records, and asthma diaries. Asthmatic patients attending our hospital's outpatient clinic are seen every 4–8 weeks and medications can only be prescribed at these appointments.

All subjects provided written informed consent, and the Ethics Committee of Fukushima Medical University approved the study.

Study Design

This was a prospective, single-center, observational study. Subjects were reviewed at entry and at intervals of 3, 6, and 12 months (four visits). At study entry, all subjects received an intensive educational program using an illustrated guide. ACT, FeNO measurements, and spirometry [FEV₁ and forced vital capacity (FVC)] were performed, and asthma control, based on the GINA guidelines, was assessed at each subsequent visit in order to evaluate the most appropriate treatment (5). Treatment remained unchanged during the first 3 months to evaluate the association of the intensive asthma educational program with asthma control. Following this 3-month period, the treatment could be changed if the subjects needed to step-up or step-down their treatment in line with the GINA guidelines (5). During the follow-up period, subjects were divided into two groups: (i) stable control group: asthmatic subjects whose treatments had not been changed or had been decreased over the study period and (ii) unstable control group: asthmatic subjects who had to increase their ICS dose or add other antiasthmatic drugs during the study period. These groups categorized as “stable” and “unstable” were used to assess ACT, FeNO, and FEV₁ as outcome predictors in this study.

Intensive Asthma Educational Program

The Ministry of Health and Welfare of Japan has developed a specific educational intervention program for asthma management according to the GINA guidelines. It provides information about asthma pathogenesis, diagnosis, severity, medications (including side effects), differences between reliever and controller agents, importance of asthma treatment, inhaler device instructions, exacerbation management, peak expiratory flow (PEF) monitoring, and a self-management plan. All subjects received a 30-min educational intervention program from a respiratory physician. The program included a detailed explanation and a demonstration of inhaler technique.

The Online FeNO Measurement Methods

FeNO measurements were made prior to spirometry at a constant flow of 50 mL/s according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines (11) using a chemiluminescence analyzer (Kimoto, Osaka, Japan). Three measurements were performed and the mean value was documented (coefficient of variation $\leq 10\%$).

Lung Function Tests

Spirometry was performed using rolling seal spirometers (CHESTAC-11; Chest M.I., Inc., Tokyo, Japan) according to the ATS guidelines (12). Three tests were performed and the highest FEV₁ was recorded. Results of FVC and FEV₁ were presented as percentages of the predicted level for statistical analysis.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 17.0; SPSS, Chicago, IL, USA). Data are shown as means and 95% confidence interval (95% CI). Changes in FeNO, ACT, and FEV₁ are shown as Δ FeNO, Δ ACT, and Δ FEV₁, respectively.

The association between intensive asthma education and asthma control was evaluated using a comparison of ACT scores, FeNO levels, and FEV₁ %predicted at study entry and at the 3-month visit using a paired *t* test. The one-way analysis of variance was used to compare changes in FeNO levels, ACT scores, and FEV₁ %predicted over 12 months in the stable and unstable asthmatic groups. Correlations of changes (Δ) and absolute levels between FeNO, ACT, and FEV₁ were evaluated using the Spearman rank correlation coefficient analysis. A receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) for each parameter was compared with 0.5 to estimate the optimal cutoff levels for detecting stable control of asthma. Sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), positive likelihood ratio (LR(+)), and negative likelihood ratio (LR(–)) were calculated. A two-tailed *p*-value of $< .05$ was considered significant.

RESULTS

Characteristic of Subjects

The study population consisted of 50 asthmatic patients with poor adherence (18 males and 32 females) (Table 1). The mean age was 55.4 years (range: 16–79 years) and the patients were nonsmokers or ex smokers with a < 5 pack-year history. Thirty-three patients (66%) were atopic and the cohort consisted of 12 mild, 21 moderate, and 17 severe persistent asthmatic subjects based on symptoms and treatment intensity (13). All the subjects were treated with regular ICS.

TABLE 1.—Subject characteristics.

Characteristics	Data
Patients	50
Sex (male/female)	18/32
Mean age (y.o.)	55.4 (50.4–60.5)
Height (cm)	157.6 (154.8–160.4)
Weight (kg)	61.1 (56.8–65.4)
Atopic status	33 (66%)
Severity of asthma	Mild persistent: 12 Moderate persistent: 21 Severe persistent: 17
FEV ₁ %predicted (%)	87.8 (81.8–93.9)
FEV ₁ /FVC (%)	72.4 (69.3–75.5)
FeNO level (ppb)	84.9 (69.6–100.1)
ACT score (point)	19.0 (18–20.1)
ICS dose (µg) BDP equivalent	1106 (957–1255)

Note: Data was expressed as mean (95% CI) or number of patients.
BDP: Beclomethasone dipropionate.

The Effect of Intensive Asthma Educational Program

Asthma treatment remained unchanged during the first 3 months. Following the educational program, a significant decrease in FeNO levels and increase in ACT scores were seen in the stable asthma group ($n = 42$) compared with the unstable asthma group ($n = 8$; $p < .001$; Figure 1A and B). There was no significant difference in FEV₁ %predicted (Figure 1C).

The Changes of FeNO Levels, ACT Scores, and FEV₁ %predicted over 12 Months

In 8 of 50 asthmatic subjects (16%), the ICS dose was increased or other antiasthmatic drugs were added due to poor asthma control. Asthma medications were decreased in 14 of 42 patients (33%) reflecting improved asthma control. Significant decreases in FeNO levels and increases in ACT score following asthma educational program remained consistent in the stable asthmatic group over the course of 12 months (Figure 1A and B).

Correlations between Absolute Levels of FeNO, ACT Scores, and FEV₁ %predicted at Each Visit

There were significant negative correlations between absolute levels of FeNO and ACT scores at the beginning of the study and at 3 months following asthma educational program ($r = -0.47$, $p = .001$; $r = -0.49$, $p = .002$, respectively) (Table 2). Negative weak correlations were found between absolute levels of FeNO and FEV₁ %predicted over the same period ($r = -0.26$, $p = .07$; $r = -0.39$, $p = .02$, respectively). However, these correlations were not present at 6 months (Table 2).

Correlations between Changes (Δ) in FeNO, ACT, and FEV₁ at Each Visit

Highly significant correlations were observed between the Δ FeNO, Δ ACT, and Δ FEV₁ which were maintained over the course of 12 months ($p < .05$; Table 3).

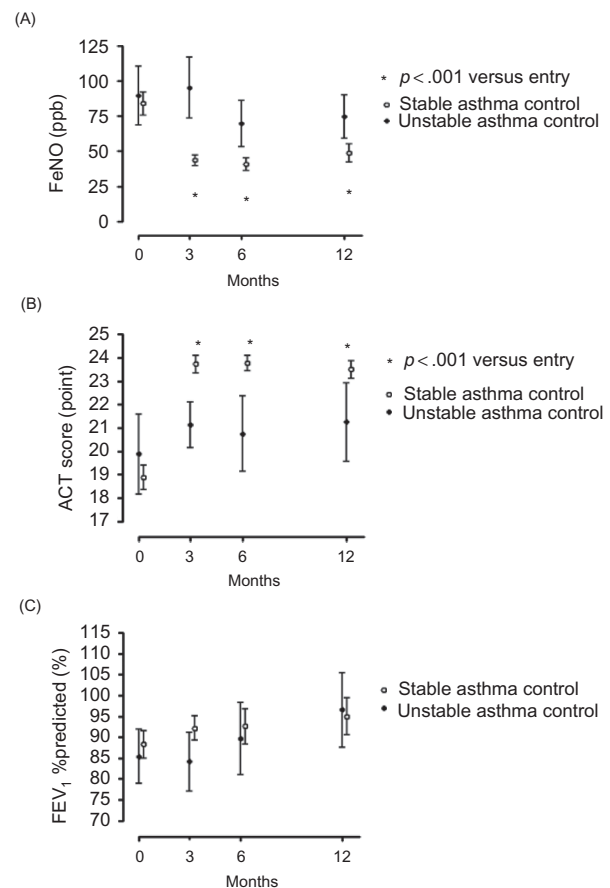


FIGURE 1.—Levels at time points indicated for FeNO levels (A), ACT score (B), and FEV₁ %predicted (C) between the subjects with or without achieving asthma control after the intensive educational interventions. Forty-two asthmatic subjects achieved good control whereas eight asthmatic subjects still had poor control.

Predictive Value of Each Parameter as a Marker to Achieve Stable Asthma Control

ROC curves were constructed to determine the cutoff levels for obtaining stable asthma control using absolute levels or changes in FeNO, ACT, and FEV₁. There were no useful parameters to discriminate subjects with stable asthma from those with unstable asthma using absolute levels (Figure 2A). However, an 18.6% decrease in Δ FeNO [AUC = 0.85, sensitivity of 80.0%, specificity of 83.3%, (LR) (+) of 4.8, LR(–) of 4.17, PPV of 92.3%, and NPV of 40%; $p = .007$] and a 3-point increase in Δ ACT (AUC = 0.794, sensitivity of 73.3%, specificity of 87.5%, LR(+) of 5.86, LR(–) of 3.28, PPV of 95.7%, and NPV of 46.7%; $p = .012$) were noted.

DISCUSSION

This is a prospective, observational study to estimate the association of asthma educational program with asthma control. We have compared the absolute levels and changes in FeNO, ACT, and FEV₁ with asthma control. Our results indicate that intensive asthma educational program may be associated with improved asthma control.

TABLE 2.—Correlations between absolute levels of FeNO, ACT scores, and FEV₁ %predicted.

FeNO	Entry	<i>p</i>	3 months	<i>p</i>	6 months	<i>p</i>	12 months	<i>p</i>
ACT	−0.47*	.001	−0.49*	.002	−0.20	.249	−0.06	.742
FEV ₁ % predicted	−0.26	.07	−0.39*	.019	−0.28	.110	−0.08	.649

Note: Spearman rank correlation coefficients were calculated and the data were expressed as *r* values.

**p* < .05.

TABLE 3.—Correlations between changes of FeNO levels, ACT scores, and FEV₁.

ΔFeNO	3-entry	<i>p</i>	6-entry	<i>p</i>	12-entry	<i>p</i>
ΔACT	−0.76*	<.001	−0.61*	<.001	−0.53*	.005
ΔFEV ₁	−0.53*	.001	−0.54*	.003	−0.42*	.03

Note: Spearman rank correlation coefficients were calculated and the data were expressed as *r* values.

**p* < .05.

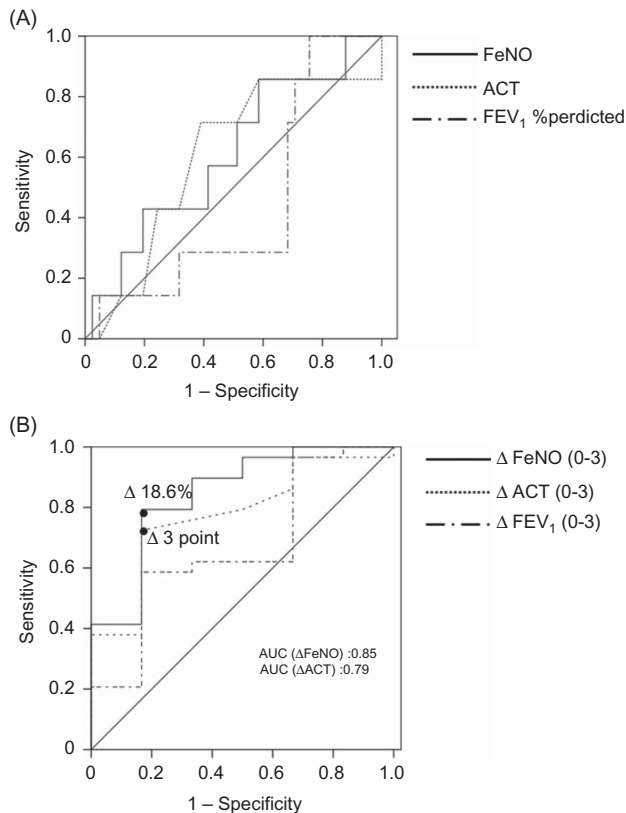


FIGURE 2.—ROC curves of absolute levels (A) and changes (B) of three parameters to determine good asthma control.

FeNO levels and ACT scores, but not FEV₁ %predicted, in the stable asthmatic group indicate improved asthma control over the course of 12 months. Changes (Δ) in FeNO levels, ACT scores, and FEV₁ had a stronger correlation, suggesting that multiple measurements and monitoring these changes may be a better way of predicting future asthma control.

Asthmatic subjects without self-management plans are often less adherent to prescribed medications and are more

likely to be poorly controlled (4, 14). Many asthmatic patients do not use their inhaler devices correctly and asthmatic patients who are more adherent to therapy are less likely to suffer exacerbations (15, 16). Therefore, asthma education plays a vital role in improving and obtaining asthma control. The GINA guidelines emphasize the importance of asthma education, highlighting that educational intervention should be an integral part of interactions between patients and physicians (5). This interaction plays an important role by increasing motivation, skills, and confidence with subsequent benefits in asthma control. This results in improved asthma symptoms and lung function, and a decreased economic burden in terms of medical expenses (17).

This study found a significant increase in ACT scores and decrease in FeNO levels at 3 months following asthma educational program in the stable asthmatic group. No significant difference was seen in the unstable asthmatic group. Several previous studies have noted similar findings, reporting that asthma education is associated with improvements in symptoms (4, 18–21), lung function (18–21), and quality of life (QOL) (19, 21). However, while some of these studies noted an association between all three factors (19,21), others found that only symptoms correlated with an educational program (4, 18, 20). This difference may be explained by the content of educational program, study designs, and characteristics of the subjects. In our study, a significant reduction in FeNO levels could be seen in the stable asthma group. There is a paucity of information regarding the relationship between asthma education and FeNO. Dressel et al. noted a significant decrease in FeNO levels and improved asthma symptoms following an educational program in occupational asthmatic patients. In addition, they found that these improvements were not correlated with lung function (22). These findings and results from our study support the view that an intensive asthma educational program may be a valuable adjunct to achieve stable asthma control.

In this study, significant decreases in FeNO levels and increases in ACT scores remained consistent over the course of 12 months in stable asthmatic subjects. Symptom questionnaires and lung function tests are recommended in the GINA guidelines as markers of asthma control (5). Although they are easy to perform on almost all subjects, they are sometimes discordant with airway inflammation (23). Furthermore, symptoms are subjective and results may be influenced by patient's perception (24). Other markers such as sputum eosinophils and AHR have shown good correlations with asthma control (25, 26). However, these tests are time consuming,

invasive, require technical skill to process, and are, therefore, difficult to incorporate into standard clinical practice. Our results suggest that a combination of ACT and FeNO may be a quick and easy way to differentiate between stable and unstable asthmatic subjects.

In this study, we found a significant relationship between Δ FeNO, Δ ACT, and Δ FEV₁ over the course of 12 months, whereas significant correlations between absolute levels were only observed at 3 months. FeNO reflects airway inflammation directly and correlates with conventional markers such as FEV₁, AHR, and sputum eosinophil counts (6–9). Several randomized control trials comparing the single or add-on effects of FeNO, with established parameters of asthma control, have only noted a limited benefit (27–30). These findings may reflect differences in study designs, the small number of subjects enrolled, variation in significance levels, and differences in asthma severity. Furthermore, individual patients may have their own personal best and range of FeNO levels, as seen with PEF measurements (31). FeNO levels in some asthmatic patients remain predominantly high regardless of an improvement in lung function and symptoms (29). Therefore, an individual cutoff level or proportional change, from baseline rather than an absolute cutoff level may be more useful.

The results of this study indicate that a 20% Δ FeNO decrease and a 3-point Δ ACT increase may predict stable asthma control. To date, few studies have examined the relationship between Δ FeNO and other conventional parameters of asthma control. Jones et al. reported that change in FeNO level from baseline had a higher PPV compared with an absolute cutoff level in terms of asthma control (32). Michils et al. suggested that a single measurement of FeNO was not a good reflection of asthma control, particularly in patients on medium-to-high doses of ICS (33). A study looking at Δ ACT found that a minimally important difference (MID) of three points is a significant predictor of asthma control (34). These studies support our observations that using changes in the levels of parameters may be better than using absolute levels for the evaluation of asthma control. We suggest that monitoring changes in FeNO levels and ACT scores in individual patients over time could be used as markers for achieving stable asthma control.

There are several limitations to this study. This is a prospective, observational study with a relatively small number of subjects tested. In addition, the educational intervention may be confounded by the Hawthorne effect, whereby subjects can subconsciously alter their behavior in a specific manner simply because of awareness of being educated and observed. Finally, subjects in this study may not represent the general asthmatic population. Only asthmatic subjects with poor adherence were recruited, and this may generate a positive selection bias. However, this is a group that we believe requires greater asthma education than their well-controlled counterparts.

In conclusion, this study suggests that comprehensive asthma educational program should be viewed as an

important treatment option and considered prior to instigating changes in treatment. In addition, the changes (Δ) in FeNO and ACT levels could become useful surrogate markers for long-term asthma management. Further, large randomized studies are warranted to determine the influence of asthma education on disease control and the utility of changes (Δ) of FeNO and ACT.

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DECLARATION OF INTEREST

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REFERENCES

- Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; 16:CD000011.
- Coutts JA, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. *Arch Dis Child* 1992; 67:332–333.
- Clerisme-Beatty EM, Bartlett SJ, Teague WG, Lima J, Irvin CG, Cohen R, Castro M, Wise RA, Rand CS. The Madison avenue effect: how drug presentation style influences adherence and outcome in patients with asthma. *J Allergy Clin Immunol* 2011; 127:406–411.
- Janson SL, McGrath KW, Covington JK, Cheng SC, Boushey HA. Individualized asthma self-management improves medication adherence and markers of asthma control. *J Allergy Clin Immunol* 2009; 123:840–846.
- Global Initiative for asthma. Global strategy for asthma management and prevention. Revised 2010. Available at: www.ginasthma.org. Accessed March 16, 2012.
- Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, Pavord ID, Ratjen F, Silkoff PE, Taylor DR, Zamel N. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest* 2010; 138:682–692.
- Saito J, Inoue K, Sugawara A, Yoshikawa M, Watanabe K, Ishida T, Ohtsuka Y, Munakata M. Exhaled nitric oxide as a marker of airway inflammation for an epidemiologic study in schoolchildren. *J Allergy Clin Immunol* 2004; 114:512–516.
- Saito J, Sato S, Hasunuma H, Ishimaru Y, Kanegae H, Kudo S, Munakata M. Off-line fractional exhaled nitric oxide measurement is useful to screen allergic airway inflammation in an adult population. *J Asthma* 2007; 44:805–810.
- Sato S, Saito J, Sato Y, Ishii T, Xintao W, Tanino Y, Ishida T, Munakata M. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. *Respir Med* 2008; 102:1452–1459.
- Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, Chang AB. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 2012; 67:199–208.
- Anonymous. 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.

12. Standardization of spirometry. 1994 update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152:1107–1136.
13. GINA Report. global strategy for asthma management and prevention. Revised 2005. Available at: www.ginasthma.org. Accessed March 16, 2012.
14. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006; 130(Suppl. 1):65S–72S.
15. Stern L, Berman J, Lumry W, Katz L, Wang L, Rosenblatt L, Doyle JJ. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. *Ann Allergy Asthma Immunol* 2006; 97:402–408.
16. Crompton GK, Barnes PJ, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, Dubus JC, Magnan A, Massone F, Sanchis J, Viejo JL, Voshaar T; Aerosol Drug Management Improvement Team. The need to improve inhalation technique in Europe: a report from the aerosol drug management improvement team. *Respir Med* 2006; 100:1479–1494.
17. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, Bauman A, Hensley MJ, Walters EH. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2003; 1:CD001117.
18. Choi JY, Cho Chung HI. Effect of an individualised education programme on asthma control, inhaler use skill, asthma knowledge and health-related quality of life among poorly compliant Korean adult patients with asthma. *J Clin Nurs* 2011; 20:119–126.
19. van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J, Assendelft WJ, Sont JK; SMASHING (Self-Management in Asthma Supported by Hospitals, ICT, Nurses and General Practitioners) Study Group. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. *Ann Intern Med* 2009; 151:110–120.
20. Kauppinen R, Vilkkä V, Sintonen H, Klaukka T, Tukiainen H. Long-term economic evaluation of intensive patient education during the first treatment year in newly diagnosed adult asthma. *Respir Med* 2001; 95:56–63.
21. Armour C, Bosnic-Anticevich S, Brilliant M, Burton D, Emmerton L, Krass I, Saini B, Smith L, Stewart K. Pharmacy Asthma Care Program (PACP) improves outcomes for patients in the community. *Thorax* 2007; 62:496–502.
22. Dressel H, Gross C, de la Motte D, Sultz J, Jörres RA, Nowak D. Educational intervention decreases exhaled nitric oxide in farmers with occupational asthma. *Eur Respir J* 2007; 30:545–548.
23. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178:218–224.
24. Lurie A, Marsala C, Hartley S, Bouchon-Meunier B, Dusser D. Patients' perception of asthma severity. *Respir Med* 2007; 101: 2145–2152.
25. Quaedvlieg V, Sele J, Henket M, Louis R. Association between asthma control and bronchial hyperresponsiveness and airways inflammation: a cross-sectional study in daily practice. *Clin Exp Allergy* 2009; 39: 1822–1829.
26. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360:1715–1721.
27. de Jongste JC, Carraro S, Hop WC, Baraldi E; CHARISM Study Group. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009; 179:93–97.
28. Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, Kattan M, Pongracic JA, Teach SJ, Bloomberg GR, Eggleston PA, Gruchalla RS, Kercsmar CM, Liu AH, Wildfire JJ, Curry MD, Busse WW. 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.
29. 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.
30. 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.
31. Smith AD, Cowan JO, Taylor DR. Exhaled nitric oxide levels in asthma: personal best versus reference values. *J Allergy Clin Immunol* 2009; 124:714–718.
32. Jones SL, Kittelson J, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, Taylor DR. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med* 2001; 164:738–743.
33. Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. *Eur Respir J* 2008; 31:539–546.
34. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the asthma control test. *J Allergy Clin Immunol* 2009; 124:719–723.