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Original Article

Optimal value of fractional exhaled nitric oxide in inhaled corticosteroid treatment for patients with chronic cough of unknown cause

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Abstract

Background: Chronic cough related to eosinophilic inflammation has become an important cause of cough in recent years. Although fractional exhaled nitrogen oxide (FeNO) measurement is an important monitoring tool, its lack of reference level may limit its usefulness. This study aimed to determine the optimal FeNO level to guide inhaled corticosteroid (ICS) management in patients with chronic cough.
Methods: This retrospective study reviewed the medical records of patients with chronic cough for more than 8 weeks. Based on the selection criteria, data were recalculated to determine the optimal cut-off value of FeNO for initiating ICS treatment in such patients.
Results: The medical records of 81 eligible patients were reviewed. Cough improved completely in 38 (Group A) of 44 patients who were treated with ICS but not in the other six patients (Group B). In the 37 patients without ICS treatment, cough improved in 32 (Group C) by specific treatment aimed at the possible causes of the cough, whereas the remaining five (Group D) had persistent cough. The patients were further subdivided into Category 1 (all patients in Group A) and Category 2 (all patients in Groups B and C). Receiver operating characteristic analysis showed that an FeNO of 33.9 ppb was the best cut-off value for using ICS (sensitivity 94.7%, specificity 76.3%) in patients with chronic cough. In fourteen of 15 patients with bronchial hyperresponsiveness (BHR) or borderline BHR, the FeNO values were equal or higher than 33.9 ppb. Obstructive ventilatory impairment was only seen in two patients.
Conclusion: Using FeNO measurement as a rapid, noninvasive diagnostic tool for patients with chronic cough, ICS can be prescribed if the FeNO is 33.9 ppb or more.

Keywords: cough variant asthma; fractional exhaled nitric oxide; inhaled corticosteroid; nonasthmatic eosinophilic bronchitis; upper airway cough syndrome

1. Introduction

Chronic cough is a complex problem with multiple causative factors. Patients are evaluated and managed in different clinical settings, ranging from primary practice to varying specialties, such as pulmonology, allergology, otorhinolaryngology, and gastroenterology, in medical centers.[1] Postnasal drip syndrome, recently referred to as upper airway cough syndrome (UACS),[2] gastroesophageal reflux disease (GERD), and cough variant asthma (CVA) are major causative factors in nonsmokers with normal chest radiographs.[3] In recent years, nonasthmatic eosinophilic bronchitis (NAEB) has become an important cause,[4] characterized by the absence of airflow obstruction and bronchial hyperresponsiveness (BHR),[5] which makes it difficult to diagnose. A recent review has demonstrated that 10−66% of coughs are due to asthma/CVA/NAEB/atopy,[6] whereas another report states that NAEB may be the cause of chronic cough in 10−30% of patients.[7] Thus, for patients with chronic cough, tests are recommended to distinguish between noneosinophilic and eosinophilic cough before initiating treatment.[8]

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A sputum differential cell count obtained from hypertonic sputum induction is a good way to diagnose NAEB but is time-consuming.[9] Exhaled nitric oxide was first reported to be elevated in asthmatic patients in 1993.[10] Subsequent studies have shown that fractional exhaled nitric oxide (FeNO) measurement is a rapid, noninvasive, reproducible tool for monitoring airway inflammation in asthmatic individuals.[11,12] Due to the high prevalence of eosinophilic inflammation-related cough, FeNO has been suggested for use in the differential diagnosis of chronic cough.[13] Hahn et al reported that FeNO can be used to predict the response to inhaled corticosteroid (ICS) treatment in chronic cough.[14]

Since FeNO level is ethnicity-dependent,[15] the lack of a national normal value may limit its usefulness. In a previous work, the reference value for FeNO was determined as 27.9 ppb.[16] Based on this result, an easy-to-remember FeNO value (30 ppb) was adapted in the present study as a criterion for initiating ICS treatment in patients with chronic cough. The purpose of this study was to evaluate this criterion and to determine an optimal FeNO level in chronic cough patients for the initiation of ICS treatment.

2. Methods

2.1. Patients

The medical records of the patients who visited the asthma and cough-specific clinic from June 1, 2007 to May 31, 2008 and who had had a history of chronic cough for more than 8 weeks were reviewed. Patients with obvious chest X-ray abnormalities, who still smoked, or who had a smoking history of more than 10 pack−years were excluded. The Institutional Review Board of Taichung Veterans General Hospital approved this retrospective study.

A stepwise approach and management protocol for chronic cough was routinely used. The first step was 1−2 weeks of a therapeutic trial period aimed at the specific complaints, such as UACS or GERD. All patients except those who stopped coughing after this period underwent FeNO measurement and a methacholine provocation test to exclude those with a possible diagnosis of classic asthma, CVA, or NAEB.

The response to treatment (i.e., complete control, improved, not improved, or worsened) and the cause of the cough was evaluated according to documentation in the medical records, in which physicians made comments based on our routinely used stepwise approach and management protocol for chronic cough. The major cause of cough was defined by the most effective treatment aimed at the related specific cause that was able to alleviate the cough completely (complete control). For diagnosing NAEB, a good response to ICS and an elevated FeNO but no BHR were the mandatory criteria. For UACS, improved symptoms of cough and upper airway symptoms (rhinorrhea, nasal block, or postnasal drip) after antihistamine or nasal corticosteroid (NCS) treatment was diagnostic. The essential element for diagnosing GERD-related cough was improved cough after proton pump inhibitor (PPI) treatment, with or without the presence of reflux symptom or esophagitis.

Online FeNO was measured using a chemiluminescence nitric oxide analyzer (NOA 280i; Sievers, Boulder, CO, USA) according to the American Thoracic Society/European Respiratory Society recommendations.[17] An expiratory flow rate of 50 mL/s for at least 10 seconds with a plateau of at least 3 seconds in duration was required. Three measurements were taken to calculate the mean FeNO level, presented in parts per billion.

The methacholine challenge test was carried out using the standard five-breath dosimeter method recommended by the American Thoracic Society.[18] The degree of BHR was determined by a provocative concentration that resulted in a 20% fall (PC_{20}) in forced expiratory volume in 1 second (FEV_1). Positive BHR was defined as $PC_{20} < 4$ mg/mL, negative BHR as $PC_{20} > 16$ mg/mL, and borderline BHR as a PC_{20} between 4 and 16 mg/mL.

ICS treatment by Fluticasone Accuhaler (GlaxoSmithKline, Greenford Middlesex, UK) with a 250 μg per dose oral inhalation of one puff twice daily was prescribed for at least 2 weeks if the cough persisted after initial symptomatic treatment and if the FeNO level was 30 ppb or more, if there was borderline to positive BHR, or if baseline ratio of FEV_1 to forced vital capacity was less than 70%.

For patients who did not receive ICS treatment or who still had a cough despite ICS treatment, further diagnostic and therapeutic steps, including NCS treatment for UACS or PPI therapy for GERD, were carried out to evaluate other possible causes. Details of other additional steps are not mentioned here because they are beyond the scope of this study.

2.2. Statistical methods

Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data were expressed as mean ± standard deviation. The nonparametric test Kruskal−Wallis H was used to analyze the variables. A p value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) of ROC analysis revealed an overall diagnostic accuracy and cut-off value of FeNO that provided the highest sensitivity and specificity. Specificity was calculated using Youden's index (defined as sensitivity + specificity − 1). Sensitivity was plotted against false positivity (1 − specificity) with the AUC performance over the diagonal line (AUC 0.5) using 95% confidence intervals (CIs).

3. Results

From 114 medical records reviewed, 26 patients were lost to follow-up after the first visit, and seven stopped coughing after the short-course (1−2 weeks) symptomatic treatment. After exclusion of these 33 patients, the remaining 81 fulfilled the inclusion criteria. Each one had validated data on FeNO measurement and a methacholine provocation test before further treatment was given. Of the 44 who received ICS treatment, there was a complete improvement of cough in 38 (Group A) but no improvement in the remaining six (Group

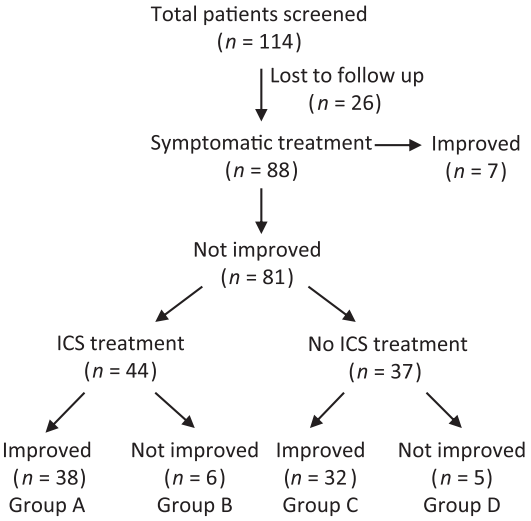

Fig. 1. Patient flow according to the diagnostic and management protocol of the study hospital. Inhaled corticosteroid treatment (ICS) resulted in complete control of the cough in 38 patients (Group A). Six patients failed to respond to ICS treatment (Group B). In 37 patients who did not receive ICS treatment, cough improved in 32 patients with other treatments (Group C). Five patients continued to have a cough without a known cause (Group D).

B). In the 37 patients without ICS treatment, cough improved completely in 32 (Group C) after management aimed at the specific cause (i.e., NCS for UACS and/or PPI for GERD). The remaining five patients (Group D) with a persistent cough were defined as having cough of unknown origin (Fig. 1).

From the general data on the 81 patients, there were 33 males and 48 females, with mean age of 49 ± 14 years. Their median duration of cough was 12 months (range 2–360 months), their mean FEV_1 was 2.6 ± 0.8 L (91.8 ± 15.3% predicted value), and their mean ratio of FEV_1 to forced vital capacity was 81.9 ± 6.3% (Table 1). There was no difference in age, duration of cough, or baseline spirometry data among the groups.

Due to the uneven distribution of FeNO levels and frequent presence of extremes or outliers, nonparametric statistical analysis by Kruskal–Wallis test was used to calculate the mean rank of the FeNO level. There was a significant difference in FeNO levels among the groups. Owing to the small case numbers in Groups B and D, only the difference in mean rank of FeNO levels between Group A (57.1 ppb) and Group C (22.4 ppb) was presented ($p < 0.005$) (Fig. 2).

Because an FeNO value of 30 ppb was the arbitrarily chosen cut-off value for initiating ICS treatment, data were subsequently analyzed and the patients were divided into two categories: Category 1 (all patients in Group A, whose cough was controlled completely by ICS) and Category 2 (all patients in the Groups B and C, whose cough did not improve after ICS treatment or whose cough improved completely without ICS). After this adjustment, the number of patients with an elevated FeNO level was reduced from 51 to 45 (Table 2). The ROC analysis determined that an FeNO of 33.9 ppb was the best cut-off value for using ICS (sensitivity 94.7%, specificity 76.3%; AUC 0.86; 95% CI 77.1–94.9%) (Fig. 3).

In terms of causes of cough, 53% of patients had multiple (at least two) causative factors (Table 3). The three leading causes of chronic cough were UACS ($n = 31$; 38.2%), NAEB ($n = 27$; 33.3%), and CVA/borderline BHR ($n = 14$; 17.3%). In contrast to the high occurrence rate of NAEB, classic asthma with obstructive ventilatory impairment was relatively rare ($n = 2$; 2.5%). Although GERD was a frequent complaint ($n = 26$; 32.1%), it was not a major cause of cough (being seen in only two patients).

4. Discussion

The evaluation and management of chronic cough of unknown origin is a complicated task. The stepwise algorithm used in the present study helps to reduce the probability of missing the diagnosis. Although some biases may exist, the data obtained from this study represent real-life experiences, which may be valuable when facing patients with a history of long-term cough.

The FeNO level reportedly correlates with sputum eosinophils or eosinophilic count obtained by bronchoalveolar lavage.[19] This makes it possible for FeNO measurement to be an alternative method of evaluating eosinophilic airway inflammation in patients with asthma or chronic cough. One

Table 1
General data of the participants.

	Group A	Group B	Group C	Group D	All
n	38	6	32	5	81
Male/female	19/19	3/3	10/22	1/4	33/48
Age (y)	49 ± 14	50 ± 12	48 ± 16	55 ± 8	49 ± 14
Median duration of cough					
Months	12	36	18	12	12
Range	2–120	2–108	2–360	2–24	2–360
Mean FEV_1, (L)	2.7 ± 0.7	2.8 ± 0.9	2.7 ± 0.9	2.1 ± 0.4	2.6 ± 0.8
Mean FEV_1 (% predicted)	89.1 ± 13.3	97.4 ± 15.1	92.8 ± 18.2	94.1 ± 19.3	91.8 ± 15.3
Mean FEV_1/FVC ratio	81.7 ± 7.3	79.5 ± 6.2	82.8 ± 5.5	80.2 ± 3.9	81.9 ± 6.3
Mean rank FeNO (ppb)[a]	57.1	59.2	22.4	16.4	47.0

Group A = cough improved after inhaled corticosteroid (ICS) treatment; Group B = cough not improved after ICS treatment; Group C = cough improved without ICS treatment; Group D = unknown cause of cough.
FeNO = fractional exhaled nitrogen oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
[a] By Kruskal–Wallis test.

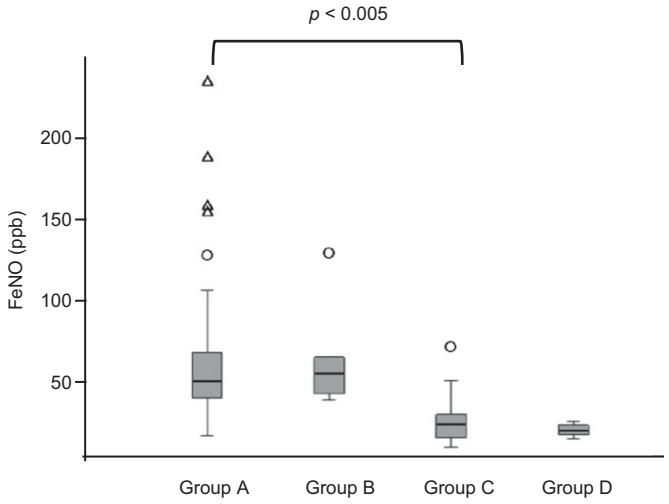

Fig. 2. The fractional exhaled nitrogen oxide (FeNO) level in the different patient groups. The transverse bars within the boxes represent the median FeNO level for each group; shaded boxes represent the 95% confidence intervals. ○ = outliers; △ = extremes.

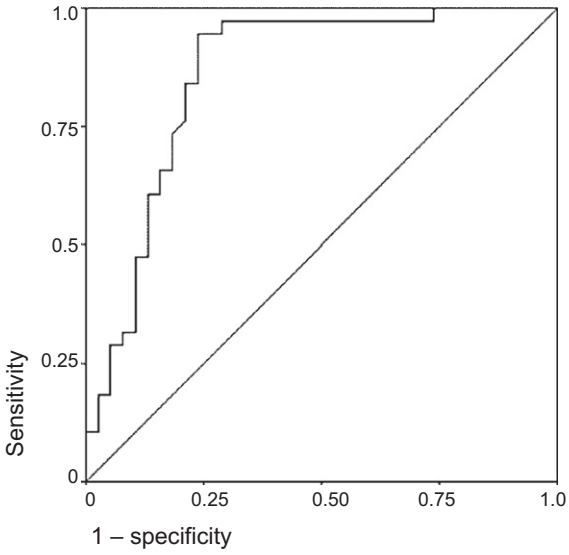

Fig. 3. The receiver operating characteristic (ROC) curve was used to assess the diagnostic accuracy and cut-off value of fractional exhaled nitrogen oxide (FeNO) level in patients with cough. The area under the curve was 0.86. An FeNO of 33.9 ppb showed the best sensitivity (94.7%) and specificity (73.8%) in predicting the effect of inhaled corticosteroids for the treatment of chronic cough.

study used FeNO $\geq$ 30 ppb as the cut-off value for diagnosing CVA, with 75% sensitivity and 87% specificity.[20] Another study suggested that NAEB could be excluded if FeNO was less than 32 ppb in patients with a chronic cough.[21] On the other hand, an FeNO of 47 ppb was reported as the lower limit for predicting corticosteroid response in chronic cough in a further study.[22]

It is known that FeNO level is ethnicity-dependent.[15] As such, the lack of a national normal value may limit its usefulness. A previous study showed that the reference normal value for FeNO was 27.9 ppb.[16] This is the basis for adopting the easy-to-remember 30 ppb of FeNO as the cut-off value in this study. However, ROC analysis after subdividing the patients into two categories revealed that an FeNO of 33.9 ppb is a better cut-off value than one of 30 ppb for predicting the response to ICS treatment. Even if there is a minimal decrease in sensitivity (from 97.4% to 94.7%), the increase in specificity (from 65.8% to 76.3%) is more pronounced. These changes have been made from the regrouping of one patient in Group A (FeNO level 31.4 ppb) and five in Group C (FeNO level range 30–32.3 ppb). Although these cut-off data are not derived from a randomized control trial, they may be useful in future for determining the timing of ICS treatment in chronic cough.

Table 2
Fractional exhaled nitrogen oxide (FeNO) level and results of treatment.

FeNO (ppb)	Category 1	Category 2			Total
	Group A (*n*)	Group B (*n*)	Group C (*n*)	Group D (*n*)	
≥30	37	6	8	0	51
<30	1	0	24	5	30
≥33.9	36	6	3	0	45
<33.9	2	0	29	5	36

FeNO cut-off value 30 ppb = sensitivity 0.974, specificity 0.658; FeNO cut-off value 33.9 ppb = sensitivity 0.957, specificity 0.763. Category 1 = all patients in Group A; Category 2 = all patients in Groups B and C.

In the present study, the causes of cough were identified not only from the history and physical examination, but also from the response to the specific treatment aimed at the possible causes. It was a unexpected finding that the number of the patients with elevated FeNO was surprisingly high, and only two patients had obstructive ventilatory impairment (2.5%).

The use of bronchodilators in patients with chronic cough is controversial.[23] Sun et al reported that oral bronchodilators are frequently used as the primary treatment method for chronic cough, especially in pediatric patients.[24] However, the oral beta-2 agonist albuterol is not recommended for patients with acute, nonspecific coughs.[25] Inhaled salbutamol has been proven to be no different from placebo in treating cough in pediatric patients.[26] Nevertheless, Irwin et al have demonstrated that an improvement in cough with bronchodilator treatment is diagnostic of CVA,[27] while the Japanese Respiratory Society guidelines for the management of cough suggest that long-acting beta-2 agonist or slow-release theophylline should be added to the treatment regimen for

Table 3
The causes of chronic cough.

	Major	Second	Third	All
Nonasthmatic eosinophilic bronchitis	27	16	1	44
Cough variant asthma	2	0	0	2
Borderline bronchial hyperresponsiveness	12	0	0	12
Classic asthma	2	0	0	2
Upper airway cough syndrome	31	21	9	61
Gastroesophageal reflux disease	2	15	9	26
Other	5	0	0	5

One cause of cough: n = 38; two causes of cough: n = 34; three causes of cough: n = 9. Major = major cause of cough; Second = secondary cause of cough; Third = tertiary possible cause of cough.

cough if ICS alone is insufficient. In the present study, the cough in two patients who presented with obstructive ventilatory impairment was controlled by combined ICS plus a long-acting beta-2 agonist.

The result of the bronchial provocation test showed a $PC_{20} < 16$ mg/mL in 14 patients. Although positive test results ($PC_{20} < 4$ mg/mL) were seen in only two patients, the remaining patients had borderline positive findings. By definition, these 12 were not classified as having CVA or NAEB, but their treatment was unaffected since they all had elevated FeNO levels.

In conclusion, this study confirms that eosinophilic inflammation of the airways is common in patients with chronic cough. FeNO measurement is a rapid and noninvasive tool that should be available in the clinic for evaluating the causes of chronic cough, and ICS treatment is indicated if the FeNO level is higher than 33.9 ppb. Further studies are indicated to validate the FeNO level and the percentage of sputum eosinophils.

References

1. Lim KG. Nitric oxide measurement in chronic cough. *Lung* 2010;**188**(Suppl 1):S19−22.
2. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**:63−71.
3. Pratter MR, Bartter T, Akers S, DuBois J. An algorithmic approach to chronic cough. *Ann Intern Med* 1993;**119**:977−83.
4. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999;**160**:406−10.
5. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *New Engl J Med* 2002;**346**:1699−705.
6. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *Lancet* 2008;**371**:1364−74.
7. Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**:S116−21.
8. Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008;**371**:1375−84.
9. Gibson PG. How to measure airway inflammation: induced sputum. *Can Respir J* 1998;**5**(Suppl A):A22-6.
10. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J* 1993;**6**:1368−70.
11. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994;**343**:133−5.
12. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax* 1998;**53**:91−5.
13. Sato S, Saito J, Sato Y, Ishii T, Xintao W, Tanino Y, et al. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. *Respir Med* 2008;**102**:1452−9.
14. Hahn PY, Morgenthaler TY, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. *Mayo Clin Proc* 2007;**82**:1350−5.
15. Olin AC, Bake B, Toren K. Fraction of exhaled nitric oxide at 50 mL/s: reference values for adult lifelong never-smokers. *Chest* 2007;**131**:1852−6.
16. Liu HC, Hsu JY, Cheng YW, Chou MC. Exhaled nitric oxide in a Taiwanese population: age and lung function as predicting factors. *J Formos Med Assoc* 2009;**108**:772−7.
17. 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;171:912−30.
18. 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**:309−29.
19. Malerba M, Ragnoli B, Radaeli A, Tantucci C. Usefulness of exhaled nitric oxide and sputum eosinophils in the long-term control of eosinophilic asthma. *Chest* 2008;**134**:733−9.
20. Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N, et al. Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med* 1999;**159**:1810−3.
21. Oh MJ, Lee JY, Lee BJ, Choi DC. Exhaled nitric oxide measurement is useful for the exclusion of nonasthmatic eosinophilic bronchitis in patients with chronic cough. *Chest* 2008;**134**:990−5.
22. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005;**172**:453−9.
23. Birring SS. Controversies in the evaluation and management of chronic cough. *Am J Respir Crit Care Med* 2011;**183**:708−15.
24. Sun HL, Lue KH, Kao YH. Prescribing patterns of anti-asthma drugs in pediatric patients. *Acta Paediatr Taiwan* 2005;**46**:212−8.
25. Littenberg B, Wheeler M, Smith DS. A randomized controlled trial of oral albuterol in acute cough. *J Fam Pract* 1996;**42**:49−53.
26. Tomerak AA, Vyas H, Lakenpaul M, McGlashan JJ, McKean M. Inhaled beta2-agonists for treating non-specific chronic cough in children. *Cochrane Database Syst Rev* 2005 (3):CD005373.
27. Irwin RS, French CT, Smyrnios NA, Curley FJ. Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. *Arch Int Med* 1997;**157**:1981−7.