ORIGINAL ARTICLE

CONTENTS

Small airways response to bronchodilators as the marker of the uncontrolled asthma in children

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ABSTRACT

Aim: To develop the criteria of small airways response to bronchodilators (by spirometry indices maximal expiratory flow (MEF50 and MEF25) as the markers of uncontrolled asthma course.

Materials and Methods: The study involved 92 participants (64 boys and 28 girls) aged 6 to 17 years (60 were less than 12 years old) with diagnosed asthma. Asthma control was assessed with the use of Asthma Control Test and Asthma Control Questionnaire. Spirometry and bronchodilator responsiveness testing were performed for all participants.

Results: Mostly, the studied children had a normal level of forced expiratory volume in the first second (FEV1), even at unsatisfactory symptoms control. The indicators of the medium and small airways patency were significantly worse in uncontrolled asthma children even in normal FEV1. Among children, the lack of asthma control can be caused by small airways obstruction in up to 80% cases. Among children who need the high dose inhaled corticosteroids treatment 93.3% have uncontrolled asthma with small airways obstruction. We found out that MEF50 and MEF25 could be the signs of the reversibility of bronchial obstruction and uncontrolled asthma with high sensitivity and specificity.

Conclusions: Indices MEF50 and MEF25 allow detecting the small airways obstruction and their reversibility as a mark of uncontrolled asthma (MEF25 has a higher diagnostic value). In case of MEF50 and/or MEF25 increasing for 22% or 25% accordingly in bronchodilator test in children, the asthma should be considered uncontrolled.

KEY WORDS: children, asthma, spirometry, reversibility, small airway dysfunction, symptoms control

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INTRODUCTION

Bronchial asthma (BA) is one of the most prevalent chronic diseases among children with high global burden. The long term goals for asthma management are good symptoms control to maintain normal activity level and future risks reduction for death, exacerbations, persistent airflow limitation and adverse events. The asthma control evaluation and its monitoring during treatment is very important [1, 2].

Asthma symptoms control assessment in children is subjective and have particularities. For example, the child can avoid physical activity to prevent feel the symptoms and does not understand his physical restriction. Children with chronic airflow limitation often do not feel dyspnea [3]. Separate symptoms evaluation is not sufficient for asthma management, even in mild course of the disease. When symptoms are absent there is a risk of severe exacerbations [1]. In some asthmatic children with good symptoms control persistent lung ventilation impairment and small airway narrowing occur [2]. Moreover, uncontrolled asthma is often a result of small airway involvement [4]. When only symptoms control is taken into account to step down the controller medication, it may lead to severe exacerbations and fixed airflow limitation in future [2].

Control of the future risks include the assessment of the exacerbations, persistent airflow limitation and therapy adverse events. Spirometry is very important tool for future risks assessment in the part of airflow limitation. At the low level of the forced expiratory volume in the first second (FEV1) the probability both exacerbations and fixed bronchial obstruction is increasing. High airway obstruction reversibility is the risk factor for asthma exacerbations. Persistent airway obstruction reversibility in the patients who take maintenance therapy is the sign of uncontrolled asthma. It is recommended for asthmatic children to perform spirometry with bronchodilator test during every visit even with normal FEV1. Positive bron-

Table 1. Demographic and anthropometric characteristics of study population

Characteristics	Mean (SD)	Median (IQR)
Age, years	10.24 (3.3)	9.5 (7.8–12.3)
Height, cm	146 (19)	143 (132–161)
Weight, kg	40.4 (17.20)	35.0 (26.8–52.5)
Body mass index, kg/m^2	18.0 (3.7)	16.8 (15.4–20.3)
Asthma duration, months	43.8 (36.9)	32 (14–60)

Abbreviations: SD – standard deviation, IQR – interquartile range.

chial obstruction reversibility test criteria for children is FEV1 increasing >12% from the start level [1]. One of the functional pattern of the spirometry in asthmatic children is the presence of the distal airway obstruction in normal FEV1 level and positive response to bronchodilator during initially normal FEV1 [3, 5, 6].

FEV1 is the indicator of the air movement through all (large and small) airways. The spirometry indices of theемнгalso should be interpreted. There is maximum mid-expiratory flow (MMEF) that is known as FEF25–75 (the forced expiratory flow at 25–75% of forced vital capacity), which reflects mid/small airways [7]. It was established that FEF25–75 increasing on 18.2% could be interpreted as positive bronchodilator test [8].

The indicators that specified small airway function are maximal expiratory flow (MEF50 and MEF25), the flows where half or 25% of forced vital capacity remains to be exhaled [9]. MEF50 and MEF25 are very important for assessment of the small airway obstruction reversibility, but the literature data how to interpret the MEF50 and MEF25 changes in bronchodilator test in children we have not found.

AIM

The aim of the study was to develop the criteria of the small airways response to bronchodilators (by spirometry indices MEF50 and MEF25) as the markers of the uncontrolled asthma course.

MATERIALS AND METHODS

ETHICS

The study was approved with the local Medical Ethics Committee of the Institute. Participants (or their legal representatives) familiarized with the study protocol and signed an informed consent form to participate in the study.

STUDY POPULATION AND DESIGN

It was observational study in children with asthma, who attended the pediatric department. The study involved 92 participants (64 (69.6%) boys and 28 (30.4%) girls) aged 6 to 17 years with diagnosed BA. Among them 60 were less than 12 years old.

Inclusion criteria: children (male and female) between 6 and 18 years old; diagnosis of asthma is based on the Global Strategy for Asthma Management and Prevention (GINA); asthma duration not less than 6 months; parent(s) or custodian signs the informed consent form before participation; ability to make acceptable spirometry performance.

Exclusion criteria: chronic respiratory illness different from asthma; other clinically significant disease.

We documented demographic, anthropometric data, asthma history, treatment, asthma control and performed spirometry with bronchodilator responsiveness test. Characteristics of patients are listed in table 1.

ASTHMA ASSESSMENT TEST AND QUESTIONNAIRE

Asthma control was assessed with the use of Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ). The ACT is a specially developed tool for assessing asthma control in children according to age: ACT-child (ACT-C) – for children from 4 to 11 years old, where there are 4 questions for the child and 3 – for parents, and the ACT – for children over 12 years old, questions of which are answered by the child. The level of the ACT and ACT-C less than 20 points indicates uncontrolled asthma (from 5 to 15 points – poorly controlled, from 16 to 19 points – not well-controlled [1, 10]). In ACQ five questions are scoring the symptoms, the sixth question asks about rescue short-acting β2-agonist, the seventh question is the pre-bronchodilator FEV1 percentage predicted. The level of the ACQ equals or more 1.5 points indicates uncontrolled asthma [11].

SPIROMETRY ASSAY

Spirometry was conducted for all participants. Before spirometry, all patients withheld from the use of short-acting bronchodilators (salbutamol – 6 hours, ipratropium bromide – 12 hour), long-acting β2-agonists

Table 2. Clinical characteristics of study population

Asthma treatment:	n (%)	Mean (SD)
ICS	49 (53.5)	
ICS + LABA	16 (17.4)	
ICS + LTRAs	14 (15.2)	
ICS + LABA + LTRAs	7 (7.5)	
LTRAs	6 (6.4)	
ICS dose (for 86 patients who receive ICS):		
Low	33 (38.4)	
Medium	38 (44.2)	
High	15 (17.4)	
ACT for 32 patients over 12 years, score		14.1 (1.6)
ACT < 20	26 (81.3)	
ACT-C for 60 patients 4–11 years, score		17.7 (4.5)
ACT-C < 20	37 (61.7)	
High dose ICS treatment (among 63 uncontrolled patients)	14 (22.2)	
ACQ, score		1.6 (0.7)
ACQ score ≥ 1.5	48 (52.2)	

Abbreviations: SD – standard deviation, ICS – inhaled corticosteroids, LABA – long-acting β2-agonists, LTRAs – leukotriene receptor antagonists.

Table 3. Spirometry results of study patients, mean (SD)

Parameters	Well-controlled (ACT 20 and more points) N=29	Not well-controlled (ACT from 16 to 19 points) N=33	Poorly controlled (ACT from 16 to 19 points) N=30
Pre BD FEV1, % of predicted values	91.8 (19.2)	86.1 (15.7)	85.4 (17.3)
Pre BD FEV1 < 80% of predicted values, n (%)	8 (27.6)	10 (30.3)	11 (33.3)
Post BD FEV1, % of predicted values	97.7 (18.8)	95.8 (16.0)	94.2 (16.5)
Post/Pre FEV1, % change	7.0 (7.8)	12.8 (12.9)*$^{p=0.039}$	11.7 (11.4)
Pre BD MEF75, % of predicted values	78.6 (26.0)	66.2 (20.9)*$^{p=0.048}$	67.5 (23.4)
Pre BD MEF75 < 80% of predicted values, n (%)	15 (51.7)	26 (78.8)	20 (66.7)
Post BD MEF75, % of predicted values	84.5 (27.5)	80.7 (21.5)	84.5 (30.6)
Post/Pre MEF75, % change	10.6 (24.7)	26.4 (30.4)*$^{p=0.031}$	27.1 (33.5)#$^{p=0.038}$
Pre BD MEF50, % of predicted values	74.7 (29.3)	63.6 (21.4)	63.7 (24.5)
Pre BD MEF50 < 80% of predicted values, n (%)	19 (65.5)	26 (78.8)	20 (66.7)
Post BD MEF50, % of predicted values	81.0 (29.1)	80.5 (25.1)	81.1 (24.9)
Post/Pre MEF50, % change	11.1 (22.8)	31.7 (34.1)*$^{p=0.007}$	37.8 (41.6)#$^{p=0.004}$
Pre BD MEF25, % of predicted values	63.8 (29.5)	60.8 (24.4)	59.2 (30,1)
Pre BD MEF25 < 80% of predicted values, n (%)	23 (79.3)	27 (81.8)	27 (70)
Post BD MEF25, % of predicted values	78.4 (34.8)	77.3 (27.5)	73.7 (33.7)
Post/Pre MEF25, % change	28.2 (43.6)	36.5 (50.2)	33.3 (42.1)

Notes. * Differences between well-controlled and not well-controlled groups significant, $p<0.05$.
Differences between well-controlled and poorly controlled groups significant, $p<0.05$.

(formoterol or salmeterol – 24 hours). Patients did not use long-acting muscarinic antagonist. Spirometry was measured using the spirometry device «MasterScreen» 'VIASYS' (Germany). Spirometry tests were performed according standardization of spirometry technical statement [12] and statement on pulmonary function testing in preschool children for six years participants [13]. Children performed spirometry seated in the upright position with the nose clips. Bronchodilator (BD) responsiveness testing performed after acceptable quality pre-dose spirometry. For the children up to 12 years old salbutamol 200 mcg and for the children

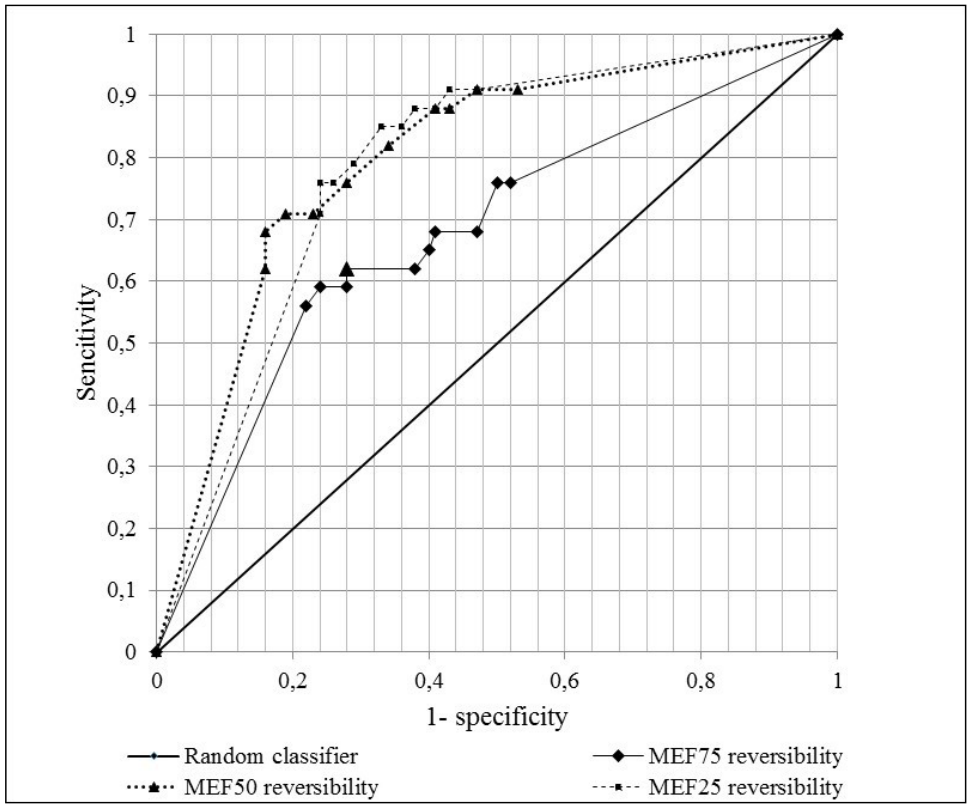

Fig. 1. ROC-curve for MEF75, MEF50 and MEF25 increasing levels as the bronchodilator responsiveness test in asthmatic children.

Table 4. Bronchodilator responsiveness test sensitivity and specificity for MEF75, MEF50, MEF25, %

Reversibility	MEF75		MEF50		MEF25	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
10.0	76.5	48.3	91.2	44.8	91.2	53.4
12.0	76.5	50.0	91.2	46.6	91.2	56.9
14.0	67.6	53.4	91.2	53.4	88.2	58.6
16.0	67.6	58.6	88.2	56.9	88.2	62.1
18.0	64.7	60.3	88.2	58.6	85.3	63.8
20.0	61.8	62.1	82.4	65.5	85.3	67.2
22.0	61.8	72.4	76.5	72.4	79.4	70.7
24.0	58.8	72.4	70.6	76.8	76.5	74.1
25.0	58.8	74.1	70.6	81.0	76.5	75.9
26.0	58.8	75.9	70.6	81.0	76.5	75.9
28.0	58.8	75.9	67.6	84.5	70.6	75.9

Table 5. Characteristics of the diagnostic test to detect the reversibility of bronchial obstruction by the use of MEF50 and MEF25

Parameters	MEF50 %(95% confidence interval)	MEF25 %(95% confidence interval)
Accuracy	73.9 (63.7 – 82.5)	76.1 (66.1 – 84.4)
Sensitivity	76.5 (58.8 – 89.3)	76.5 (58.8 – 89.3)
Specificity	72.4 (59.1 – 83.3)	75.9 (62.8 – 86.1)
Positive predictive value (+PV)	61.9 (50.7 – 72.0)	65.0 (53.2 – 75.3)
Negative predictive value (-PV)	84.0 (73.7 – 90.8)	84.6 (74.7 – 91.1)

after 12 years – salbutamol 400 mcg were used. In 15 minutes after salbutamol inhalation postBD spirometry was performed. Only acceptable measurements were included into analyses. The following spirometry parameters were evaluated: FEV1, MEF75, MEF50, MEF25. All data were presented as percentage of predicted values.

STATISTICAL ANALYSIS

Data collection and statistical analysis were carried out by licensing software products included in the package Microsoft Office Professional using mathematical and statistical functions MS Excel. The studied parameters were evaluated by determining the mean and standard deviation (SD) or median with interquartile range (IQR) for quantitative variables. For the comparison of spirometry results differences in groups with different asthma control, the Student's t test (two-sample, independent samples t-test) was applied. We compared the spirometry parameters means. Verification of numerical series for compliance with the normal distribution was carried out using the special function NORMSAMP_1, developed for the Excel program.

To analyze the characteristics of the diagnostic test, 2×2 tables were built. Accuracy, sensitivity, specificity, positive predictive value (+PV) and negative predictive value (-PV) were calculated [14]. The evaluation of the diagnostic test was conducted with receiver operating characteristic (ROC) curve analysis. The ROC curve charts were built with the use QI Macros add-in for Excel [15]. Area under ROC curve (AUC) was calculated [16].

RESULTS

Asthma treatment and asthma control are listed in table 2. The majority of children received inhaled corticosteroids (ICS) low and medium doses. The most children had uncontrolled course of BA. Among 15 patients who need high doses ICS treatment, 14 (93.3%) had uncontrolled asthma.

We divided patients into three groups by the ACT. There were well-controlled (ACT 20 and more points), not well-controlled (ACT from 16 to 19 points) and poorly controlled (ACT from 5 to 15 points) groups. Spirometry results are presented in table 3.

On average, the studied children had normal level of FEV1, even at the presence of unsatisfactory symptoms control. However, the indicators of the medium and small airways patency significantly worsened in children with uncontrolled asthma even in normal FEV1. The most notable airflow limitation in the middle and small bronchi occurs not in poorly, but in partially controlled group. With symptoms control worsening, more pronounced response to bronchodilator is observed not only for FEV1, but also for medium and small airways. Thus, the indicators of small airway obstruction and their response to bronchodilator can serve as markers of uncontrolled asthma.

During bronchodilator test MEF75, MEF50 and MEF25 increase to significant level not only in patients with an increase in FEV1 by 12.0% or more, but in patients in which FEV1 reversibility varies between 6.0 and 11.9%. It can be assumed that the increase in MEF75, MEF50 and MEF25 during bronchodilator test can confirm the presence of reversible bronchial obstruction in asthmatic children who do not reach the FEV1 increasing by 12.0% or more. In order to define the diagnostic criteria for the bronchial obstruction reversibility, data about the increase in FEV1 (as reference method) and MEF75, MEF50, MEF25 were analyzed. Among the percentage of MEF75, MEF50, MEF25 increasing, the following reference points were analyzed: 10.0; 12.0; 14.0; 16.0; 18.0; 20.0; 22.0; 24.0; 25.0; 26.0 and 28.0% from the level before the inhalation of the bronchodilator as a measure of bronchodilator responsiveness.

It was found that for MEF reversibility level 12.0% after bronchodilator test inherent high sensitivity and low test specificity. At the levels MEF reversibility 14.0, 16.0 and 18.0% after bronchodilator the specificity becomes higher. During test specificity is increasing the sensitivity is falling. If we considered 26.0 or 28.0% as the marker of MEF reversibility, the sensitivity is decreasing without specificity improving (table 4).

To determine the best diagnostic point of MEF75, MEF50, MEF25 increasing in the terms of determining the reversibility of bronchial obstruction in children with asthma, we conducted the ROC analysis. As the ROC curves show (fig. 1), the best point for MEF75 reversibility is 22.0% and more with sensitivity 61.8% and specificity 72.4%. For MEF50 the best point of the bronchodilator reversibility level is also 22.0% with the sensitivity 76.5% and specificity 72.4%. In the case of MEF25, increasing by 25.0% in the bronchodilator test is the marker of bronchial obstruction reversibility with the sensitivity 76.5% and specificity 75.9%.

AUC displays the quality of the diagnostic test while the value 0.9–1.0 means excellent, the value 0.8–0.9 means good, 0.7–0.8 – moderate and 0.6–0.7 means unacceptable quality [16]. In our study AUC for MEF75 reversibility is 0.680, for MEF50 and MEF25 are 0.808 and 0.802 accordingly and such test with the use of MEF75 is less acceptable for clinical practice. Thus, the bronchial obstruction reversibility assessment by MEF50 and MEF25 increasing in bronchodilator responsiveness test has high quality regarding AUC data.

The next step of our study was to analyze the characteristics of the diagnostic test to detect the reversibility of bronchial obstruction by the use of MEF50 and MEF25. To do this, patients were divided into those who had or did not have reversible bronchial obstruction, and 2×2 tables were built. It was found that MEF50 shows the accuracy of the test 73.9%. The prognostic value is high both for the positive result – 61.9% and for negative – 84.0% (table 5). There is no minimum

required sensitivity or specificity for diagnostic tests. However, tests, the sensitivity and specificity of which do not reach 50%, are unacceptable in practice [16]. In our case, the sensitivity and specificity are high – 76.5 and 72.4%, respectively.

When evaluating MEF25, the accuracy of the test was 76.1%, the prognostic value of the test is 65.0% for positive result and 84.6% for negative. Confidence intervals of the calculated characteristics of the diagnostic test confirm its high quality, because in no case the limit of the confidence interval is reduced to below 50%.

DISCUSSION

Isolated symptoms score is not sufficient for the asthma control assessment even with standard questionnaire. Interestingly, in our study the uncontrolled asthma by ACT observed in 63 patients. At the same time among these patients only 48 were uncontrolled by AQC. We explain this as normal FEV1 in the answer for seventh point of the questionnaire reduced the mean value of the poor symptoms.

We focused on the knowledge that obstruction at the level of small airways in children has significant negative effect on the course of BA. It is increasing the frequency and severity of attacks, bronchial hyperresponsiveness to physical exertion and weather factors, which lead to ineffective control of BA, even in patients receiving standard maintenance therapy. Significant bronchodilator responsiveness in patients taking maintain therapy may indicate uncontrolled asthma. Any diagnostic test is useful in conditions of uncertain diagnosis. If it is necessary to detect the reversibility of bronchial obstruction in children, considering the criteria of MEF50 and MEF25 is particularly attractive. On the one hand, it is a part of routine spirometry without involving other diagnostic interventions. On the other hand, MEF50 and MEF25 reflect small airway dysfunction.

The small airways bronchodilator responsiveness in asthma patients has been the subject of interest of various researchers and heterogeneous studies are conducted in this field. As small airways are affected early in obstructive lung diseases, their assessment may be a part of future risk control in asthma management [17].

One of our main findings that in children with uncontrolled BA during spirometry FEV1 is often normal, but MEF75, MEF50 and MEF25 are considerably decreased. This is corresponds with other authors that the reason of the luck of asthma control is small airway dysfunction [18, 19]. The prevalence of small airway dysfunction in asthma patients is 50–60% and observed in all GINA step classes [20]. It is interesting that in the work of Bao W. et al the small airway dysfunction (namely MEF50 and MEF25 decreasing) had such background as violation of the histological structure of the lung tissue despite normal CT imaging and normal FEV1 [21]. However, current literature data regarding small airways dysfunction mainly belong to adults, while we investigate the small airways as the indicator of the uncontrolled asthma course in children from 6 years.

Other our result is establishing relationship between response to bronchodilator of the FEV1 and MEF. The literature data how to interpret the MEF changes in bronchodilator test in children we have not found. We reveal not only FEV1 increasing after bronchodilator is a mark of uncontrolled asthma, but MEF50 and MEF25 post bronchodilator changes indicate this. We were able to calculate the spirometry indices of the reversibility of bronchial obstruction according to the MEF50 and MEF25. When MEF50 increase in the bronchodilator test equal to or greater than 22% and MEF25 increase equal to or greater than 25% it is sensitive in the detection of the losing of asthma control. For MEF50 the accuracy of the test is 73.9%, sensitivity – 76.5%, specificity – 72.4%, area under the ROC curve is 0.808, (for MEF25 – 76.1%, 76.5%, 75.9% and 0.802, respectively), which corresponds to the high quality of the diagnostic test to determine the reversibility of bronchial obstruction. In comparison two parameters: MEF50 and MEF25, the last has the best quality because of higher accuracy, specificity and predictive value.

Thus, evaluation of the clinical and functional status of the patient is important in asthma management. The lack of asthma control in children can be caused by small airways obstruction in up to 80% cases. Among children who need the high dose ICS treatment 93.3% have uncontrolled asthma with small airways obstruction. Further research in larger population-based studies is needed to establish generally accepted parameters for bronchodilator responsiveness testing of small airways to implement them in routine clinical practice.

CONCLUSIONS

1. It is recommended for asthmatic children to perform spirometry with bronchodilator test during every visit even with normal FEV1.
2. When interpreting the results of spirometry in children with bronchial asthma, the level of MEF50 increase in the bronchodilator test equal to or greater than 22% of the value before taking a bronchodilator (or MEF25 increase level equal to or greater than 25%) is proposed as a sign of reversibility of bronchial obstruction.
3. For MEF50 the accuracy of the test is 73.9%, sensitivity - 76.4%, specificity - 72.4%, area under the ROC

curve 0.808, (for MEF25 – 76.1%, 76.5%, 75.9 % and 0.802, respectively), which corresponds to the high quality of the diagnostic test.
4. Spirometry indices MEF50 and MEF25 allow detecting the small airways obstruction and its reversibility is a mark of uncontrolled asthma. Herewith index MEF25 has higher diagnostic value.
5. In case of MEF50 and/or MEF25 increasing for 22% or 25% accordingly in bronchodilator test in children the asthma should be considered uncontrolled.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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