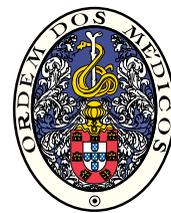


Fractional Exhaled Nitric Oxide in Monitoring and Therapeutic Management of Asthma



Fração Exalada de Óxido Nítrico no Controlo e Abordagem Terapêutica da Asma

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ABSTRACT

Introduction: Asthma is a chronic respiratory disease characterized by hyper-responsiveness and bronchial inflammation. The bronchial inflammation in these patients can be monitored by measuring the fractional exhaled nitric oxide. This study aims to determine fractional exhaled nitric oxide association with peak expiratory flow and with asthma control inferred by the Global Initiative for Asthma.

Material and Methods: Observational, analytical and cross-sectional study of children with asthma, 6-12 years-old, followed in the Outpatient Respiratory Pathology of Braga Hospital. Sociodemographic and clinical information were collected through a questionnaire. Fractional exhaled nitric oxide and peak expiratory flow were determined by portable analyzer Niox Mino[®] and flow meter, respectively.

Results: The sample is constituted by 101 asthmatic children, 63 (62.4%) of males and 38 (37.6%) females. The mean age of participants in the sample is 9.18 (1.99) years. The logistic regression performed with the cutoff value obtained by ROC curve, revealed that fractional exhaled nitric oxide ($b_{FENO\ classes} = 0.85$; $\chi^2_{Wald}(1) = 8.71$; OR = 2.33; $p = 0.003$) has a statistically significant effect on the probability of changing level of asthma control. The odds ratio of going from "controlled" to "partly controlled/uncontrolled" is 2.33 per each level of fractional exhaled nitric oxide.

Discussion: The probability of an asthmatic children change their level of asthma control, from 'controlled' to 'partly controlled/uncontrolled', taking into account a change in their fractional exhaled nitric oxide level, increases 133%.

Keywords: Child; Asthma; Exhalation; Nitric Oxide; Portugal.

RESUMO

Introdução: A asma é uma doença respiratória crónica caracterizada pela hiper-reatividade e inflamação brônquica. A inflamação brônquica destes doentes pode ser monitorizada através da medição da fração exalada de óxido nítrico. Este estudo tem por objetivo determinar a associação do valor da fração exalada de óxido nítrico com o débito expiratório máximo instantâneo e com o controlo da asma determinado pela Classificação da Iniciativa Global para a Asma.

Material e Métodos: Estudo observacional, analítico e transversal de crianças com asma, 6-12 anos, seguidas na Consulta Externa de Patologia Respiratória do Hospital de Braga. Informação sociodemográfica e clínica colhida através de um questionário. Determinado o valor da fração exalada de óxido nítrico, através do analisador portátil Niox Mino[®], e do débito expiratório máximo instantâneo, através do debitómetro.

Resultados: A amostra é constituída por 101 crianças asmáticas, 63 (62,4%) do sexo masculino e 38 (37,6%) do sexo feminino. A idade média dos participantes na amostra é de 9,18 (1,99) anos. A regressão logística, realizada com o valor de *cutoff* obtido pela curva de ROC, revelou que a fração exalada de óxido nítrico tem um efeito estatisticamente significativo ($b_{Níveis\ do\ FENO} = 0,85$; $\chi^2_{Wald}(1) = 8,71$; OR = 2,33; $p = 0,003$) sobre a probabilidade de mudar de nível de controlo da asma. Por cada nível de fração exalada de óxido nítrico incrementado o *odds* de passar a não controlada é 2,33 vezes superior.

Discussão: A probabilidade de uma criança asmática mudar o seu nível de controlo da asma, de 'controlada' para 'parcialmente controlada/não controlada', tendo em consideração uma alteração no seu nível da fração exalada de óxido nítrico, aumenta 133%.

Palavras-chave: Criança; Asma; Expiração; Óxido Nítrico; Portugal.

INTRODUCTION

Asthma is a chronic respiratory disease characterized by bronchial hyper-responsiveness and inflammation.^{1,2} Major asthma signs and symptoms include dyspnea/shortness of breath, wheezing, chest tightness and cough.³ The pathophysiology of inflammation involves several cells and inflammatory mediators, mainly eosinophil, macrophage, cytokines, cysteinyl leukotrienes and nitric oxide.³⁻⁵ Chronic airway inflammation is related to bronchial hyper-reactivity in response to several stimuli, mainly dust mites, pollens, tobacco smoke and air pollution,³ leading to generalized airway obstruction and consequently to airflow reduction.

Asthma is estimated to affect approximately 300 million people world-wide.^{6,7} It is the most common chronic disease affecting children.⁸ According to the National Health Enquiry (*Inquérito Nacional de Saúde*) 2005/2006, in Portugal, there is a paediatric asthma prevalence in children aged under 15 of 4.94%.⁹

Asthma has an individual, familial and socio-economic impact.¹⁰ When uncontrolled, it results in school absenteeism, loss in life quality and to an increase in costs when compared with controlled asthma.^{3,10}

Nitric oxide was detected for the first time in exhaled

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air in 1991¹¹ and is produced by bronchial epithelium.¹² Fractional Exhaled Nitric Oxide (FeNO) has been studied over the past few years due to the importance of precise monitoring and evaluation of the inflammatory process, as in asthma symptoms and signs as well as respiratory function reduction are unspecific and do not necessarily reflect the underlying inflammatory process.¹³ In addition, airway inflammation may be present regardless of the presence or absence of symptoms, the disease phenotype, disease activity or remission^{10,14-16} unlike bronchial obstruction which is spontaneously or therapeutically reversible.³ It is therefore essential to search for techniques that enable monitoring of airway inflammatory status, in order to allow for improved follow-up and early detection of exacerbations or uncontrolled asthma.

FeNO measurements may be affected by factors such as patient's age, gender, atopy, tobacco smoke, nitrate-rich food, respiratory infections, oral/inhaled glucocorticoid and leukotriene antagonist medications.^{11,16-22}

One of the methods allowing for the evaluation of airway inflammation is bronchial biopsy, an expensive and invasive examination which is not routinely feasible.^{16,23} Another method involves induced sputum, but many children are unable to expel secretions as a result of which the procedure becomes very time-consuming.¹⁶ Unlike these two methods, FeNO measurement is simple, non-invasive and provides quickly obtainable results.²⁴ Several studies revealed a positive correlation between FeNO, bronchial biopsy results^{15,25} and sputum analysis.²⁶⁻²⁸

In 2011, the American Thoracic Society (ATS) reached the conclusion that FeNO has a major role in airway eosinophil inflammation detection, in corticosteroid response determination and in airway inflammation monitoring, in order to determine the indication for corticosteroid use and to check for patient's compliance to the latter.²⁹

FeNO increase in children has been referred to as an asthma worsening predictive factor upon corticosteroid

withdrawal.^{30,31}

In 2009, the ATS identified the utility of FeNO measurement as an instrument for monitoring asthma control and clarified the relationship between FeNO and other asthma control parameters, defining the strategy for the present study.³²

We aimed to assess the relationship between FeNO value, peak expiratory flow (PEF) and asthma control as determined by the GINA (Global Initiative for Asthma) classification.

MATERIAL AND METHODS

This is an observational, analytical and cross-sectional study carried out in the Department of Paediatrics at the *Hospital de Braga (HB)*. Our group of patients included a selected sample of 101 children with asthma, aged between six and twelve, followed in Out-patients, at the *Consulta Externa de Patologia Respiratória (CEPR)* of the HB. Children were non-randomly selected.

Inclusion criteria included: children aged between six and twelve diagnosed with asthma and followed at the CEPR of the HB.

Exclusion criteria included: children aged under six or above twelve, not followed at the CEPR of the HB and not accepting to participate in the study and those children without an asthma diagnosis (Fig. 1).

A confidential anonymous questionnaire was designed and completed by the researcher, and included children and parents' demographic, therapeutic and asthma control characteristics. Asthma control level (controlled, partly controlled and uncontrolled) was determined according to the response to five questions based on the GINA classification.³

The questionnaire was pre-tested with ten children with asthma before the study was started. Informed consent was obtained from each child's legal representative.

Instantaneous determination of FeNO was obtained using a Niox Mino[®] electrochemical portable analyser

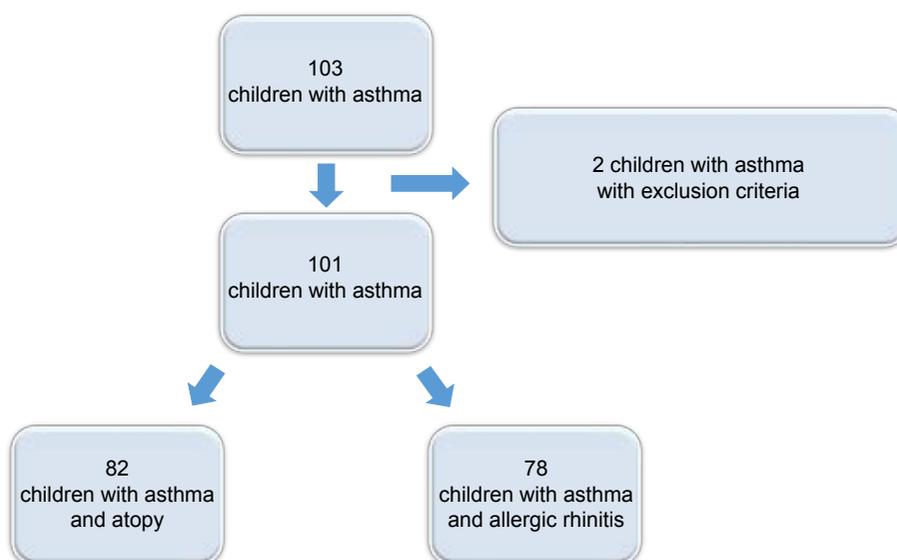


Figure 1 – Flowchart of study population

(Aerocrine, Sweden)³³⁻³⁶ following ATS and European Respiratory Society (ERS) recommendations.³⁷ A single FeNO measurement was obtained for each child with asthma^{38,39} and the expiratory flow was measured for six seconds.^{40,41}

Upon FeNO determination, PEF value was obtained with the peak-flow meter following ATS/ERS guidelines.⁴² PEF measurement was repeated three times and the highest value was recorded.⁴³ This value was compared to normal paediatric reference values.⁴⁴

The patient's body weight, height and abdominal circumference were determined according to the *Guia de*

*Avaliação do Estado Nutricional Infantil e Juvenil.*⁴⁵

The study was approved by HB's Executive and Ethics Committee.

Data were analysed with IBM SPSS Statistical v.20 software. Continuous variable normality was analysed using Kolmogorov-Smirnov and Shapiro-Wilk tests⁴⁶ and we opted to use non-parametric tests for FeNO and PEF variables. Sample characterisation was done using descriptive statistics (frequency distribution, central tendency measures and dispersion measures). The association between ordinal qualitative variables was analysed using Spearman ordinal correlation coefficient. Logistic regression and ROC

Table 1 – Descriptive analysis regarding therapy and asthma control

		n (%)	Mean (SD)
FeNO classes*:			
• Low		0 (0)	
• Normal		36 (35.6)	
• Intermediate		17 (16.8)	
• High		48 (47.5)	
Value of FeNO (ppb)			38.19 (27.74)
Value of PEF** (L/min)			194.36 (61.06)
Therapy:			
• Short-acting β 2-agonists		0 (0)	
• Inhaled corticosteroids (IC)		25 (24.8)	
• Leukotriene-receptor antagonists (LTRA)		23 (22.8)	
• Long-acting β 2-agonists		0 (0)	
• Theophylline		0 (0)	
• Oral glucocorticoid		0 (0)	
• Immune therapy		1 (1)	
• No medication		34 (33.7)	
• IC + Long-acting β 2-agonists		4 (4)	
• IC + Long-acting β 2-agonists + LTRA		4 (4)	
• IC + LTRA		10 (9.9)	
Current respiratory infection (last 4 weeks)	Yes	15 (14.9)	
Over the last 4 weeks:			
• Day-time symptoms more than twice/week	Yes	22 (21.8)	
• Night-time symptoms/arousals	Yes	12 (11.9)	
• Daily activities or exercises constrained by asthma	Yes	41 (40.6)	
• Need for relief-medication more than twice/week	Yes	9 (8.9)	
• < 80% from PEF expected value	Yes	49 (48.5)	
GINA classification***:			
• Controlled		28 (27.7)	
• Partly controlled		59 (58.4)	
• Partly controlled		14 (13.9)	

* Fractional exhaled nitric oxide; ** Peak expiratory flow; *** Global Initiative for Asthma

(receiving operating characteristics) curve design was used to assess the level of significance of FeNO, atopy, allergic rhinitis and current respiratory infection (CRI) regarding the odds of having a 'controlled' or 'partly controlled/uncontrolled' control level according to the GINA classification.

The CRI variable was defined as the presence of a respiratory infection over the last four weeks.

Questions regarding the level of asthma control were defined as: presence of day-time symptoms suggesting asthma, more than twice a week, over the last four weeks; presence of night-time symptoms suggesting asthma, over the last four weeks, presence of daily activity restrictions over the last four weeks; daily medication requirement beyond chronic medication more than twice a week over the last four weeks; PEF value measured with the peak-flow meter of less than 80% of the expected value.

The FeNO variable was classified as: low FeNO when < 5 ppb (part per billion), normal FeNO when < 21 ppb, intermediate FeNO – 21-35 ppb and high FeNO - > 35 ppb.^{32,39}

Asthma control variables were divided in three levels: controlled, partly controlled and uncontrolled, according to GINA classification.

A p -value < 0.05 was considered as statistically significant

RESULTS

From the 103 patients eligible for our study, only two refused to participate. Therefore, our group included 101 children with asthma, 63 (62.4%) male. Mean age (SD) was 9.18 (1.99). Most patients presented atopy ($n = 82$; 81.2%), allergic rhinitis ($n = 78$; 77.2%), abdominal circumference percentile (P) < 75 ($n = 59$; 58.4%) and were living in a rural area ($n = 56$; 55.4%).

Mean FeNO value was 38.19 (27.74) ppb and most patients were classified as in the normal ($n = 26$; 35.6%) and high FeNO class ($n = 48$; 47.5%). Regarding therapy, most patients were not on any medication ($n = 34$; 33.7%). Regarding asthma control, the results revealed that most

patients were partly controlled, ($n = 59$; 58.4%) (Table 1).

Most parents did not smoke and did not have a family history of atopy. However, we found a small percentage of mothers smoking ($n = 10$; 9.9%), and a higher percentage of mothers with an atopic family history ($n = 33$; 32.7%). A history of atopy was more frequent in the maternal ($n = 54$; 53.5%) than the paternal side of the family ($n = 46$; 45.5%).

In our study there was no correlation between FeNO and PEF values, $r_s = 0.154$, $p = 0.125$. On the contrary, there was a significant, moderately positive correlation, according to Cohen classification,⁴⁸ between the GINA Classification and the FeNO classes, $r_s = 0.405$, $p < 0.001$.

Regarding therapy, children with asthma treated with inhaled corticosteroids (IC) alone show a lower FeNO value when compared to children on a leukotriene receptor antagonist (LTRA), IC + LTRA or to children on no medication (Fig. 2).

The percentage of patients in each group, according to the FeNO classes and the GINA classification is presented in Fig. 3. Most patients with controlled and uncontrolled asthma, according to GINA, are correctly classified by FeNO classes (64.29% and 92.86%, respectively). However, the patients with partly-controlled asthma are mostly classified in high and normal FeNO classes (45.76% and 28.81%, respectively).

Logistic regression using a cut-off value obtained by the ROC curve, aimed to maximize sensibility and specificity, revealed that CRI ($b_{CRI} = 0.94$; $\chi^2_{Wald}(1) = 1.25$; $p = 0.263$), atopy ($b_{Atopy} = 0.26$; $\chi^2_{Wald}(1) = 0.13$; $p = 0.723$) and allergic rhinitis ($b_{Allergic\ rhinitis} = 1.07$; $\chi^2_{Wald}(1) = 1.89$; $p = 0.169$) did not show a statistically significant effect on the odds of changing asthma control level. On the other hand, FeNO class variables ($b_{FeNO\ class} = 0.85$; $\chi^2_{Wald}(1) = 8.71$; OR = 2.33; $p = 0.003$) has a statistically significant effect (Table 2). The odds ratio of changing from 'controlled' to 'partly controlled/uncontrolled' is 2.33 for each FeNO class, i.e. when a child changes from a certain FeNO class to another, the odds ratio to change from 'controlled' to 'partly controlled/uncontrolled' show a 133% increase, according

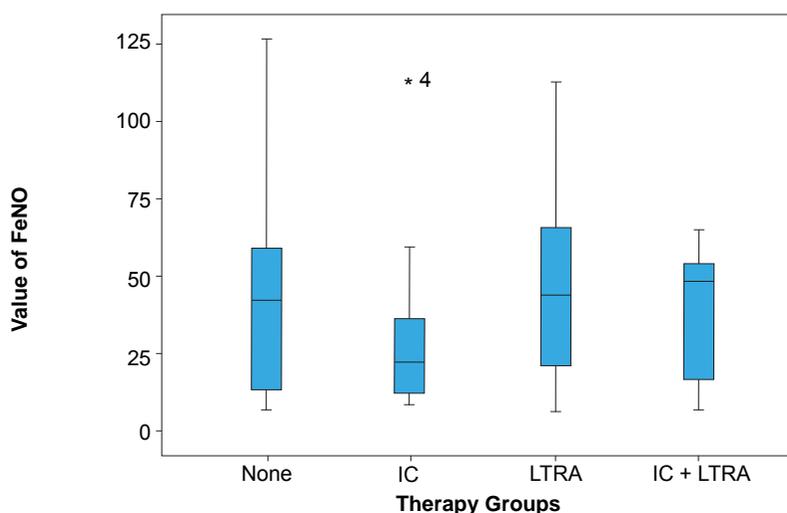


Figure 2 – Values of FeNO according to the therapy group

Table 2 – Logistic regression model coefficients of GINA Classification*, according to FENO classes**, CRI***, atopy and allergic rhinitis.

	B	Std Error	χ^2_{Wald}	p value	OR	95% CI
FeNO classes	0.85	0.29	8.71	0.003	2.33]1.33; 4.10[
CRI	-0.94	0.83	1.25	0.263	0.39]0.08; 2.02[
Atopy	0.26	0.73	0.13	0.723	1.29]0.31; 5.35[
Allergic rhinitis	1.07	0.78	1.89	0.169	2.92]0.63; 13.40[
Constant	-0.98	1.21	0.65	0.420	0.38	-

* Global Initiative for Asthma; ** Fractional exhaled nitric oxide; *** Current respiratory infection.

Table 3 – Observed and estimated classification of children with asthma (cut-off value is 0.739)

		GINA classification*		%
		Controlled	Partly controlled / uncontrolled	
INA classification	Controlled	18	10	64.3
	Partly controlled / uncontrolled	22	51	69.9
Global percentage				68.3

* Global Initiative for Asthma

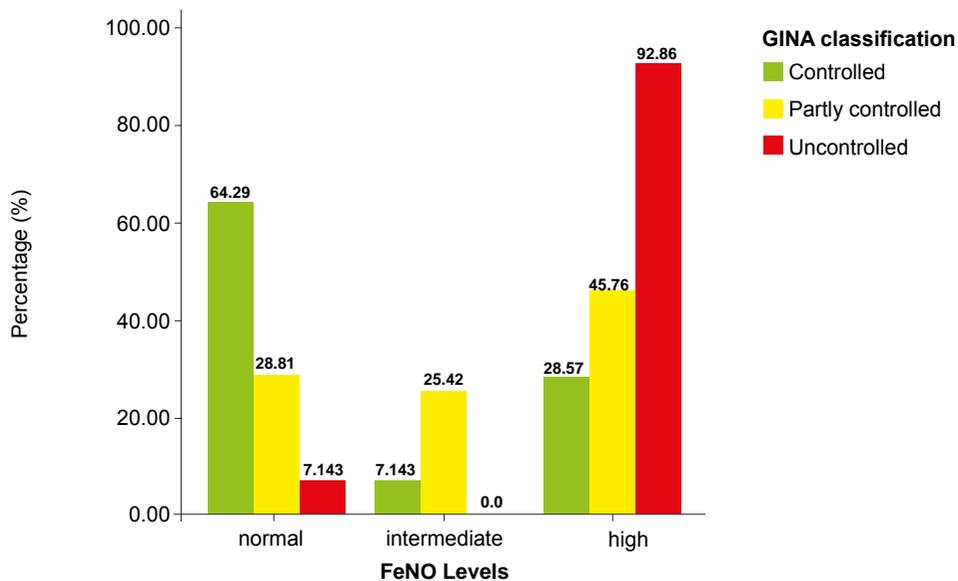


Figure 3 – Percentage of children with asthma according to asthma control levels and FeNO classes

to the expression % Odds ratio = $100 \times [\exp(\beta_j) - 1]$.⁴⁶ This logistic regression model is significant [$G^2(df) = 15.799$, $p < 0.001$; Nagelkerke $R^2 = 0.209$]. Patients were also classified and we obtained a correct classification percentage of 68.3% (Table 3). This value is considerably higher than the proportional percentage of a correct classification

obtained by chance (59.9%). According to Hosmer and Lemeshow,⁴⁹ the sensitivity (69.9%), specificity (64.3%) (Table 3) and an acceptable discriminative capacity (ROC $c = 0.745$; $p < 0.001$) were obtained.

DISCUSSION

The treatment of asthma is aimed to reach and maintain disease clinical manifestations under control for long periods of time,³ although some studies have shown that this objective has yet to be reached.^{50,51} The GINA classification aimed to help doctors with asthma control, divides the patients into three levels: controlled, partly controlled and uncontrolled. However, this classification does not involve an airway inflammation objective assessment. Therefore, investing and exploring new techniques is an essential issue, allowing for further knowledge regarding asthma control in a simple and quick way and FeNO is one of these examples, according to recent literature.

In our study, children with asthma aged between six and twelve were assessed. The lower age limit was chosen because despite asthma symptoms being common in pre-school ages, these are usually temporal⁵² and also because the GINA classification differentiates asthma diagnoses above the age of six. The upper age limit was defined by operational and cost control reasons.

In the study, most patients with asthma were male, in line with what has been described in several studies.^{3,52-55} Most children, (58.4%) have no abdominal obesity-related increased risk ($p < 75$), present in 19.8% ($p > 90$). Unlike what has been described by Bacharier *et al.*,⁵² asthma prevalence is not higher in children with a family history of atopy.

The present study shows that there is no correlation between the values of FeNO and PEF, in line with the study by Pijnenburg *et al.*⁵⁶ This result may be explained according to the assessment of asthma control signs using FeNO, which assesses airway inflammation, and using PEF, which assesses lung function. Therefore, the two tests complement each other in asthma control evaluation.

This study shows a moderately positive and statistically significant correlation⁴⁸ between asthma control levels established by GINA and FeNO classes.

One of the results obtained with this study showed that most children with asthma on daily corticosteroid treatment present lower FeNO values than children on other medication. These results are in line with those referred in The European Respiratory Monograph by Alving and Malinovschi.⁵⁷

Regarding Fig. 3, one possible explanation for some children classified with GINA as partly controlled or uncontrolled but which are placed in normal level based on FeNO classification may be due to the fact that FeNO is not satisfactorily correlated to neutrophil-mediated inflammation.^{10,58} We emphasize that FeNO values may be significantly affected by some factors which were not excluded in the present study, such as medication with inhaled corticosteroid, allergic rhinitis, current respiratory infection and feeding, which may partially explain the fact that some children classified under GINA as controlled or partly controlled are classified in higher levels when comparing with FeNO classes.

In our study, we did not obtain FeNO absolute values that would predict the loss of asthma control but rather the odds of a child with asthma to change from being no longer controlled to being partly/uncontrolled, according to the GINA criteria. According to logistic regression using a cut-off value obtained from the ROC curve, the change of level of asthma control is not significantly affected by CRI, atopy or allergic rhinitis. However, FeNO class variables have a statistically significant effect on the odds of a child with asthma changing control levels. When a child with asthma changes FeNO level there is a 133% increase in the chance of switching from a 'controlled' level to a 'partly/uncontrolled level'. We have obtained a 68.3% percentage regarding the correct classification of children with asthma, i.e. 68.3% of children are correctly classified by the three levels of FeNO. This value is 59.9% higher than the proportional percentage of correct classifications obtained by chance, showing the utility of the model in classifying new observations. The ROC curve presents an acceptable discriminative capacity⁴⁹ with a sensitivity of 69.9% and a specificity of 64.3%.

One can describe some limitations to this study, namely the use of a convenience sample and the non-exclusion of children with asthma with characteristics that might affect FeNO measurements; however, these inclusions allow for the maintenance of usual clinical practice issues and to obtain results that may be extrapolated to the general population of children with asthma and not only to the group of children with asthma that did not have those characteristics;¹⁷. Other constraints to the study include the daily variability of PEF⁵⁹ and the possible bad execution of the technique by the child. However, in the absence of an assessment instrument of asthma control validated for the Portuguese child population, we have decided to assess patients according to the GINA guidelines that included PEF measurement using a peak-flow meter.

CONCLUSION

This study showed that most children with asthma in our group of patients, have their disease controlled or partly controlled.

There is a positive correlation between the levels of asthma control established by the GINA classification and FeNO levels. However, there is no correlation between FeNO values and PEF values.

The odds-ratio of a child with asthma to change his level of asthma control, from 'controlled' to 'partly/uncontrolled', taking into account a change in FeNO level, is affected by a 133% increase.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SOURCES

There were no external financial sources for writing this manuscript.

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