

CORRELATION BETWEEN FENO VALUE AND ASTHMA SEVERITY

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ABSTRACT

Objective. The purpose of this study is to assess the correlation between the FeNO (fractional exhaled nitric oxide) value and asthma severity.

Material and method. A prospective study including 48 children aged 5 to 18 years, who have been diagnosed with asthma in „Victor Gomoiu” Children Clinical Hospital between May 2012 – November 2013, has been initiated.

In the first stage of the study both the diagnosis and the degree of severity of asthma, using GINA 2008 guideline criteria, have been established, and the FeNO value has been measured before beginning any controller therapy.

For the persistent asthma forms the controller therapy has been initiated, adapted to provide the controlled asthma status.

In the next stage, after GINA 2014 guideline was published, a second classification of asthma, based on the degree of severity, has been performed, by taking into account the treatment step necessary to maintain the controlled asthma status, according to this new guide.

Finally the correlation between FeNO value and the degree of asthma severity has been assessed, using first the asthma classification from GINA 2008 guideline and then the asthma classification from GINA 2014 guideline.

Results. Among those 48 children included in the study 29 had normal FeNO value and 19 elevated FeNO value. According to GINA 2008 guideline criteria they have been included in the following severity asthma forms: 6 patients intermittent asthma, 27 patients mild persistent asthma, 14 patients moderate persistent asthma and 1 patient severe persistent asthma.

According to GINA 2014 guideline criteria 25 patients have been labeled as mild asthma, 22 as moderate asthma and 1 as severe asthma.

The statistic assessment of the correlation between asthma severity form according to GINA 2008 guideline and FeNO value provided a value of $p = 0,278$ and for the correlation between FeNO value and asthma severity form according to GINA 2014 guideline provided a value of $p = 0,0468$.

Conclusion. FeNO value is not correlated with asthma severity as resulted from GINA 2008 guideline classification, but is correlated with asthma severity as resulted from GINA 2014 guideline classification.

Keywords: asthma, severity, FeNO, asthma form

INTRODUCTION

Asthma is a chronic inflammatory condition of the airways, which represents a major cause of mortality and morbidity, having a continuous increase of incidence in the entire world (6).

Asthma is a very heterogeneous disease which can express various phenotypes of clinical features with variable treatment response.

The physiopathological features of asthma are represented by chronic bronchial inflammation and

bronchial hyperresponsiveness, expressed as bronchoconstriction in response to various triggers (12).

Both of them underlie the variable airflow limitation, clinically displayed as wheezing, breath shortness, chest tightness and cough (6).

The airflow limitation can follow an intermittent or persistent pattern and can vary in frequency and intensity with time, related to the exposure to specific triggers and to the treatment response (4). All of these features have a contribution in defining the degrees of asthma severity.

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Bronchial asthma management is based on the correct diagnosis of asthma assessment, on triggers identification and their control and on the personalized and adapted treatment plan, addressed to both asthma exacerbations and to control therapy, and on periodically evaluations.

Asthma management presumes also a proper assessment of asthma severity for each patient.

Until recently asthma classification by degrees of severity was made only considering the daytime and nighttime symptoms, the limitation of daily activities, the use of reliever medication (short acting beta agonist), the FEV1 (forced expiratory volume in one second) and/or PEF (peak expiratory flow) values (5).

Over time a discrepancy was noted between the degree of difficulty to achieve the controlled asthma status, with proper controller treatment, and the degree of asthma severity assessed using only clinical features and respiratory testing results.

Therefore the need for a new classification of asthma severity was emphasized, which should include the assessment of controller therapy response (6).

Even today is still difficult to predict the response pattern to controller treatment for each patient before initiating and directly assessing the controller treatment response.

Numerous studies attempted to identify the predicting factors for therapeutic response and, thus, for asthma severity (7,10).

Atopy is one of those predicting factors, identified in over 50% of asthma cases in children; the association with atopy is much stronger for severe asthma (3,4,12).

FeNO (fractional exhaled nitric oxide) is a non-invasive biomarker of eosinophilic bronchial inflammation, specific for asthma, which is closely linked with atopy (8,9,11,13).

For these reasons the objective of this study was to assess the correlation between FeNO value and asthma severity, in other words to determine if FeNO is a predictor of asthma severity.

MATERIAL AND METHOD

A prospective study including 48 children aged 5 to 18 years, who have been diagnosed with asthma in „Victor Gomoiu” Children Clinical Hospital between May 2012 – November 2013, has been initiated.

Inclusion criteria were:

1. age between 5 and 18 years;
2. asthma diagnosis established using specific criteria of history and clinical exam; diagnosis was

confirmed by proving FEV1 reversibility of at least 12% after salbutamol inhalation;

3. lack of any controller therapy before the patients inclusion in the study.

Exclusion criteria: other coexistent comorbidities.

In the first stage of the study, the diagnosis for each patient has been established and consequently the form of asthma has been labeled, by accounting the daytime and nighttime symptoms, the exacerbations, the limitation of daily activities, the use of reliever medication (short acting beta agonist), the FEV1 values and/or PEF values, according to GINA 2008 guideline criteria (Global Initiative for Asthma, 2008), as presented in Table 1.

TABLE 1. Asthma severity forms according to GINA 2008 guideline

SEVERITY	CHARACTERISTICS
INTERMITTENT	Symptoms < 1/week Short exacerbations Nighttime symptoms < 2/month FEV1 or PEF \geq 80% from predicted FEV1 or PEF variability < 20%
MILD PERSISTENT	Symptoms > 1/week, but < 1/day Exacerbations can limit activity or sleeping Nighttime symptoms > 2/month FEV1 or PEF \geq 80% from predicted Variability 20-30%
MODERATE PERSISTENT	Daily symptoms Exacerbations can limit activity or sleeping Nighttime symptoms >1/week Daily use of SABA FEV1 or PEF 60-80% from predicted Variability > 30%
SEVERE PERSISTENT	Daily symptoms Frequent exacerbations Frequent nighttime symptoms Limitation of physical activity FEV1 or PEF \leq 60% from predicted Variability > 30%

At the same time the FeNO value has been measured using NIOX-MINO with mouth piece, a chemiluminescence analyzer approved for exhaled nitric oxide measurement (2,5,6). Normal values for pediatric age vary between 5-25 ppb.

In the next stage, for each included patient, an asthma action plan has been drawn, which contains personalized prescriptions and recommendations addressed to the control of triggers and to the use of reliever medication (step 1 of treatment, SABA, short acting beta agonist, inhaled salbutamol).

Moreover for those patients with persistent asthma form has been initiated the controller therapy beginning with step 2 of treatment. (5).

Depending on asthma form, either intermittent or persistent, has been established a schedule of

both clinical and respiratory testing evaluations, as listed below:

- patients with intermittent asthma: evaluation after one month, after three months, six months and one year after the diagnosis was made, beside evaluation in case for asthma attacks;
- patients with persistent asthma: evaluation after one month, after three months, six months and one year after the diagnosis was made and controller therapy was initiated.

After 3-6 months since initiating the controller therapy the asthma control status has been assessed. By accounting the FEV1 value, the history of symptoms from the last month and the use of reliever medication, has been established the asthma control status for each patient individually, pointing if in that moment asthma was controlled, partially controlled or uncontrolled (5).

For those who had uncontrolled or partially controlled asthma, appropriate interventions have been applied (triggers control, controller step-up) and the evaluations schedule has been followed once more, until the controlled asthma status was achieved.

In the next stage, after GINA 2014 was published, a new classification of included asthmatic patients has been performed, based on the degrees of severity for each patient individually, by accounting the step of controller treatment required to maintain the controlled asthma status, as showed in this new guide and in the Table 2.

TABLE 2. Asthma severity forms according to GINA 2014 guideline

SEVERITY	CHARACTERISTICS
MILD	Necessity for step 1 or 2 for asthma control
MODERATE	Necessity for step 3 for asthma control
SEVERE	Necessity for step 4 or 5 for asthma control

Finally the correlation between FeNO value and asthma severity, as it was established according to both GINA 2008 guideline criteria and GINA 2014 guideline criteria, were assessed.

RESULTS

Among the patients included in the study 29 had normal FeNO value (≤ 25 ppb), and 19 had increased FeNO value (> 25 ppb).

According to GINA 2008 criteria for establishing the asthma severity form, 6 patients had intermittent asthma, 27 had mild persistent asthma, 14 had moderate persistent asthma and 1 had severe persistent asthma.

The distribution of patients in each category of asthma severity, established using GINA 2008 classification criteria, along with the distribution of the patients according to FeNO values, are depicted in Table 3.

TABLE 3. Patients distribution based on asthma severity form according to GINA 2008 guideline and on FeNO value

ASTHMA SEVERITY (GINA 2008)	FeNO < 25 ppb	FeNO \geq 25 ppb	TOTAL
INTERMITTENT	3	3	6
MILD PERSISTENT	19	8	27
MODERATE PERSISTENT	6	8	14
SEVERE PERSISTENT	1	0	1
TOTAL	29	19	48

Using the Chi-Square Test statistical function, the correlation between the FeNO value and the all four category of asthma severity according to GINA 2008 guideline, as they were depicted in Table 3, has been assessed, and a p value of $p = 0.278$ (no statistical significance) has been obtained.

According to GINA 2014 guideline classification criteria for assessing the asthma severity form, by accounting the controller therapy step required to achieve the controlled asthma status, 25 patients met the criteria for mild asthma, 22 for moderate asthma and 1 for severe asthma.

The distribution of patients in each category of asthma severity, established using GINA 2014 guideline classification criteria, along with the distribution of the patients according to FeNO values are depicted in Table 4.

TABLE 4. Patients distribution based on asthma severity form according to GINA 2014 guideline and on FeNO value

ASTHMA FORM GINA 2014	FeNO < 25 ppb	FeNO \geq 25 ppb	TOTAL
MILD	19	6	25
MODERATE	10	12	22
SEVERE	0	1	1
TOTAL	29	19	48

Using the Chi-Square Test statistical function the correlation between the FeNO value and all four categories of asthma severity according to GINA 2014 guideline, as they were depicted in Table 3, has been assessed, and a p value of $p = 0.04468$ (statistical significant) has been obtained.

The correlation between asthma severity forms, established according to both GINA 2008 guideline and GINA 2014 guideline classification criteria, is depicted in Table 5.

TABLE 5. Patients distribution based on asthma severity form according to GINA 2008 guideline and GINA 2014 guideline

ASTHMA FORM GINA 2008/GINA 2014	MILD	MODERATE	SEVERE	TOTAL
INTERMITTENT	6	0	0	6
MILD PERSISTENT	15	12	0	27
MODERATE PERSISTENT	4	9	1	14
SEVERE PERSISTENT	0	1	0	1
TOTAL	25	22	1	48

Using the Chi-Square Test statistical function the correlation between the asthma severity forms established according to GINA 2008 guideline and asthma severity forms established according to GINA 2014 guideline, as they were depicted in Table 5, has been assessed, and a p value of $p = 0.0719$ (no statistical significance) has been obtained.

DISCUSSIONS

The classification of asthma based on the degrees of severity according to GINA 2008 guideline is accomplished by accounting the daytime and nighttime symptoms, the exacerbations, the limitation of daily activities, the use of reliever medication and the FEV1 and PEF values.

We already know that more than one half of the asthmatic children have atopic asthma phenotype and that the most severe asthma cases are recruited from atopic asthma patients. Besides that FeNO is an atopy biomarker. However in our study FeNO value is not correlated with asthma severity the way it was established using GINA 2008 guideline criteria ($p = 0.278$ not statistically significant).

When using the degrees of asthma severity by taking account of the treatment response, as it happened when we classified asthma cases using GINA 2014 guideline criteria, we have obtained a statistically significant correlation ($p = 0.0468$) between asthma severity and FeNO value. In other words an increased FeNO value is related to an increased asthma severity.

This result is following up the current recommendations concerning the use of FeNO for identifying the responsiveness to the corticosteroids used as controller therapy (2).

The validity of this result is additionally confirmed by the current definition of severe asthma, the way it was established by the European Respiratory Society/American Thoracic Society consensus, in which the response to controller therapy is taken into account (1); it also postulates that severe asthma is a difficult to treat asthma. Thus is additionally emphasized the strong connection between asthma severity and the pattern of treatment response.

Therefore an increased FeNO value predicts a difficult response to treatment and, by that, a severe asthma form.

For an additional confirmation of this result the correlation between the two severity categories, as they were established using separately the two classifications systems, is not statistically significant ($p = 0.0719$).

CONCLUSIONS

1. There is no correlation between asthma severity assessed using only clinical features and respiratory function parameters and asthma severity assessed by taking into account the step of treatment necessary to maintain the controlled asthma status.
2. There is no correlation between FeNO value and asthma severity assessed using only clinical features and parameters of respiratory function.
3. FeNO value is correlated with asthma severity assessed by taking into account the step of treatment necessary to maintain the controlled asthma status.
4. An increased FeNO value predicts a severe asthma form, meaning that it predicts an asthma form who needs a superior treatment step in order to achieve the controlled asthma status.

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