THE UTILITY OF MEASURING FENO IN MONITORING ASTHMATIC CHILDREN

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ABSTRACT

Purposes and objectives. Bronchial asthma is the most frequent chronic disease in children and in almost 50% of these cases, it occurs eosinophilic airway inflammation. The most important objective in monitoring asthma is preventing exacerbations by means of good communication between phisician, patient and family, a good compliance of the latter and an accurate assesment of the asthmatic patient's quality of life. Present study is examining correlation between asthma control and airways eosinophilic inflammation level in asthmatic children treated with ICS.
Method and material. We evaluated 24 patients presented in emergengy department of our hospital, during ten weeks in cold season. The assesment consisted in performing Asthma Control Test (ACT), measuring fraction of the exhaled nitric oxide (FeNO) and pulmonary function testing.
Results and discussions. We documented a negative linear correlation of ACT score with FeNO (r = -0. 6286 (p < 0.01)).
Conclusions. Measuring FeNO is a simple to perform, fast and noninvasive method. FeNO value is related to ACT score, between them being a negative linear correlation. Generating simple algorithms may improve control of disease and tailoring therapy asthmatic children.

Keywords: ACT score, FeNO, monitoring, child

INTRODUCTION

Nitric oxide (NO) is produced by three isoforms of NO synthase utilizing l-arginine as substrate: iNOS (inducible), eNOS (endothelial), nNOS (neuronal) (1). eNOS and nNOS are being stimulated by increased intracellular Ca (2+) and iNOS is being stimulated by the inflammatory citokines. (2).

Exhaled nitric oxide has been dubbed an „inflammometer" because of the elevated levels found in exhaled air when airway inflammation occurs. (3). The fiberoptic bronchoscopy in asthmatic patients points out that NO is derived from the lower respiratory tract. (4).

Exhaled nitric oxide levels decrease when NOS enzymes or inhaled corticosteroids are given. (13).

FeNO levels can be increased in asthmatic patients. It reflects eosinophilic-mediated inflammatory pathways moderately well in central and/or peripheral airway sites and implies increased inhaled and systemic corticosteroid responsiveness (14). FeNO is reduced in cystic fibrosis and primary ciliary dyskinesia. (15).

BACKGROUND AND AIM OF STUDY

Bronchial asthma is the most frequent chronic disease in children and in almost 50% of these cases, it causes eosinophilic airway inflammation, emphasized by studies of noneosinophilic asthma. (5,6). The most important objective in monitoring asthma is preventing exacerbations by means of good communication between physician, patient and family, a good compliance of the latter and an accurate assesment of the asthmatic patient's quality of life. Present study is examining correlation between asthma control and airways eosinophilic inflammation level in asthmatic children treated with ICS, being already known that there is a good correlation in adults between the two variables.

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TABLE 1. *Factors affecting exhaled and nasal NO measurements in healthy subjects (16)*

Increased NO	Decrease NO
Pharmacologic Papaverin, Sodium nitroprusside, L-arginine, ACE inhibitors	Oxymetazoline, NOS inhibitors
Physiologic and procedural Arginine ingestion, nitrate- enriched food	Repetead spirometry acute and transient after forced exhalation, physical exercise, menstrual cycle, sputum induction, body temperature reduction
Environmental, occupational Air pollution (NO, ozone)	Water vapour, CO_2, nitrous oxide
Occupational hazards Fluoride dust, ozone, chlorine dioxide, rubber latex, formaldehyde exposure, electromagnetic field generated by cellular phone	100% inspired O_2, moderate altitude
Habitual	Smoking, alcohol ingestion
Infections	URTI
ACE – angiotensin – converting enzyme,	URTI – upper respiratory tract infection

TABLE 2. *Interpreting FeNO values (17)*

Low feno (< 25 ppb (< 20 ppb in children)): implies noneosinophilic or no airway inflammation	**High feno (> 50 ppb (>35 ppb in children)) or rising feno (> 40% change from previously stable levels): implies uncontrolled or deteriorating eosinophilic airway inflammation**
Diagnosis In a symptomatic patient (chronic cough and/or wheeze and/or shortness of breath for > 6 wk) presenting for the first time, the patient is unlikely to benefit from a trial of inhaled corticosteroid treatment **Possible etiologies**: **Other pulmonary/airway causes:** - Rhinosinusitis - Noneosinophilic asthma - Reactive airways dysfunction syndrome - COPD - Bronchiectasis - Cystic fibrosis, - primary ciliary dyskinesia - Extended post-viral bronchial hyperresponsiveness syndrome - Vocal cord dysfunction **Nonpulmonary/airway causes:** - Anxiety-hyperventilation - Gastroesophageal reflux disease - Cardiac disease/pulmonary hypertension/pulmonary embolism **Confounding factors:** - Smoking - Obesity **Monitoring In a symptomatic patient with an established diagnosis of asthma, possible etiologies:** - Asthma: - Noneosinophilic asthma (probably steroid unresponsive) **Additional or alternative diagnosis** - Vocal cord dysfunction - Anxiety-hyperventilation - Bronchiectasis - Cardiac disease - Rhinosinusitis, - Gastroesophageal reflux disease **In an asymptomatic patient with an established diagnosis of asthma:** Implies adequate dosing and good adherence to antiinflammatory therapy Inhaled corticosteroid dose may possibly be reduced (repeat FENO 4wk later to confirm this judgment).	**Diagnosis** In a symptomatic patient (chronic cough and/or wheeze and/or shortness of breath during past > 6 wk) presenting for the first time, **possible etiologies**: - Atopic asthma - Eosinophilic bronchitis - COPD with mixed inflammatory phenotype That the patient is likely to benefit from a trial of inhaled corticosteroid treatment. **Monitoring In a symptomatic patient with an established diagnosis of asthma, possible etiologies:** - High persistent allergen exposure - Inhaled corticosteroid delivery problems: Poor adherence, Poor inhaler technique, proximal drug deposition, with untreated distal airway/alveolar inflammation - Inadequate inhaled corticosteroid dose *Likely to respond to increased inhaled corticosteroid dose OR prednisone* **Rarely:** - truly steroid resistant asthma - Churg Strauss syndrome, - pulmonary eosinophilia **In an asymptomatic patient:** No change in inhaled corticosteroid dosing, but refer to FENO trend over time in individual patient. Withdrawing inhaled corticosteroid is likely to be followed by relapse. An increase in therapy is indicated as some patients are asymptomatic, but the high FENO could be a risk factor for an upcoming exacerbation. "High" FENO may be normal in a certain percent of the population.
COPD chronic obstructive pulmonary disease. The interpretation of FENO is an adjunct measure to history, physical exam, and lung function assessment.	

TABLE 3. *General outline for FeNO interpretation (17).*

General outline for FENO interpretation: symptoms refer to cough and/or wheeze and/or shortness of breath			
	FENO < 25 ppb (<20 ppb in children)	FENO 25-50 ppb (20-35 ppb in children)	FENO > 50 ppb (> 35 ppb in children)
DIAGNOSIS			
Symptoms present during past 6 wk	- Eosinophilic airway inflammation unlikely - Alternative diagnoses - Unlikely to benefit from ICS	- Be cautious - Evaluate clinical context - Monitor change in FENO over time	- Eosinophilic airway inflammation present - Likely to benefit from ICS
Monitoring (in Patients with Diagnosed Asthma)			
Symptoms present	- Possible alternative diagnoses - Unlikely to benefit from increase in ICS	- Persistent allergen exposure - Inadequate ICS dose - Poor adherence - Steroid resistance	- Persistent allergen exposure - Poor adherence or inhaler technique - Inadequate ICS dose - Risk for exacerbation - Steroid resistance
Symptoms absent	- Adequate ICS dose - Good adherence ICS taper	- Adequate ICS dosing - Good adherence - Monitor change in FENO	- ICS withdrawal or dose reduction may result in relapse - Poor adherence or inhaler technique

(21,23,24) Recent data are suggesting a possible correlation also in asthmatic children. (20,25), with a higher sensitivity and specificity of ACT to FENO in identifying not well controlled cases. (26). Non-invasive assessment methods are being considered for other types of high risk asthma patients, for example pregnant women. (29). Nowadays concern for this area of research is revealed in the 687 papers in Pubmed since 2010 (32). FeNO contribution as a non invasive method for assessing airway eosinophilic inflammation caused the responsible authorities – National Institute for Health and Care Excellence (NICE) – to incorporate FeNO in the UK 2014 Practical Guidelines (30).

METHODS AND MATERIALS

We have selected patients according to the following inclusion criteria:

- Diagnosis of Bronchial Asthma * (ICD 10, 2014 – J45).
- Patient with mild, moderate, severe persistent asthma.
- Age below 18 years when presented to Emergency Department (ED) of our hospital.

Four patients have been excluded from the study because of impossible or inaccurate performance during FeNO evaluation in spite of age (6-8 years old) that was appropriate for well understanding of method (with good explanations).

We have proven a good correlation of ACT with FENO in a young woman presenting to ED for exacerbation, having no current controller medication. The results haven't been included in our study

For measuring FeNO, we used NObreath® ENO Tester, that consists of:

- LCD monitor
- Antibacterial filter with unidirectional valve
- Mouthpieces that contain two filters that keep exhaled air dry for the test's accuracy.

The device measures the level of exhaled NO in parts per billion (ppb), electrochemical sensing.

The patient breaths quietly for 5 minutes

The mouthpiece is being attached to Nobreath flow and then everything attached to the monitor. After selecting a pediatric test the patient breaths in then puts the mouthpiece into his mouth pressing the lips firmly on the piece and starts exhaling after the beep signal. The monitor must be held upright at all times during a breath test a certain time indicated by the monitor (10 sec). The metallic ball in the NObreath flow should be kept within the white band in the center of the tube during the test. The mouthpieces are single-patient use and can be used for a maximum of 3 attempts. The final value of FeNO is the greatest value of the 3 readings.

The collecting data method tracked the following features of the group:

- Physical examination, performing ACT score
- Usual vital functions monitoring
- Measuring FeNO
- Performing pulmonary functional tests
- Asthma Control Test score (ACT) (18).

It is a questionnaire that consists of 5 single-answer questions, used to asses asthma control. Elements of asthma evaluation are defined by de NHLBI (National Heart, Lung and Blood Institute): severity, control and responsiveness to treatment.

1. In the past 4 weeks how much of the time did your asthma keep you from getting as much done at work, school or at home?

FIGURE 1. *Measuring FeNO in a patient*

1) All the time 2) Most of the time 3) Some of the time 4) A little of the time 5) None of the time.

2. During the past 4 weeks how often have you had shortness of breath?

1) More than once a day 2) Once a day 3) 3 to 6 times a week 4) Once or twice a week 5) Not at all.

3. During the past 4 weeks how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

1) 4 or more nights a week 2) 2 or 3 nights a week 3) Once a week 4) Once or twice 5) Not at all

4. During the past 4 weeks how often have you used rescue inhaler or nebulizer medication (such as albuterol)?

1) 3 or more times per day 2) 1 or 2 times per day 3) 2 or 3 times per week 4) Once a week or less 5) Not at all

5. How would you rate your asthma control during the past 4 weeks?

1) Not controlled at all 2) Poorly controlled 3) Somewhat controlled 4) Well controlled 5) Completely controlled

The final score results by adding each question's score (the figure before the question):

< = 5, uncontrolled asthma

5-19 poorly controlled asthma

> = 19 well controlled asthma

25 perfect controlled asthma

The test is correlated with the pulmonary function tests. Test-retest reliability is 0.77.

RESULTS

Patients that met inclusion criteria during these ten weeks were mostly boys, aged between 6-17 years. The adult patient was female. According to American Academy of Allergy Asthma & Immunology and CDC, male children have an increased incidence of asthma-like symptoms, with a switch of this ratio in adult life (19).

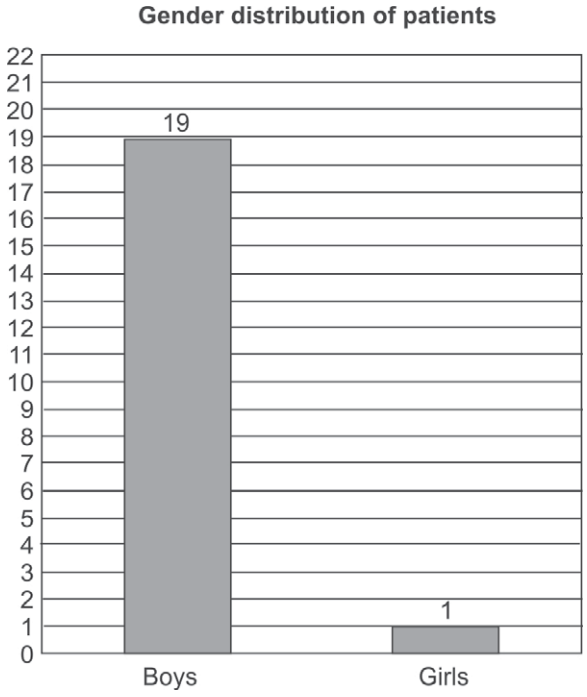

FIGURE 2. *Gender distribution of patients*

Out of the 20 enrolled patients, one has a low ACT score of 17, documenting uncontrolled asthma. Patient exhibited an incorrect way of medication self-administration rather than incompliance. Dosage and schedule of medication were kept the same but inhalation technique was demonstrated and both patient and his mother were trained again with a tutorial dry-powder device.

5 patients had a borderline ACT score of 20-21. One of these patients had an unexpectedly low FeNO level of 3 ppb, in the other four ACT scoring being influenced by a recent exacerbation.

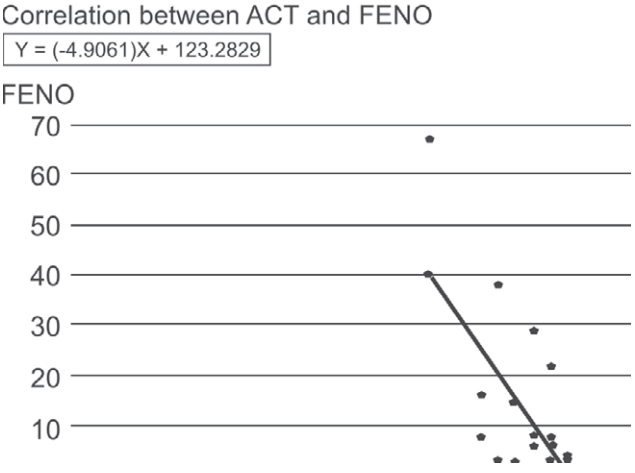

FIGURE 3. *Correlation between ACT score and FeNO (Epi Info 7)*

Means

	Obs	Total	Mean	Var	Std Dev	Min	25%	Median	75%	Max	Mode
ACT	20	451	22.55	4.26	2.06	17.00	21.00	23.00	24.00	25.00	24.00

Means

	Obs	Total	Mean	Var	Std Dev	Min	25%	Median	75%	Max	Mode
FENO	20	253	12.65	259.50	16.11	0.00	3.00	6.00	15.50	67.00	3.00

FIGURE 4. *Average values and standard deviation for FeNO and ACT score*

All other 14 patients had a well-controlled asthma with an ACT score 22-25.

Value of ACT score was correlated with FeNO in a linear and negative way (r = -0.6286).

We checked if this correlation is statistically significant by calculating (with Microsoft Office Excel 2007 and Epi Info 7) degrees of freedom (d.f.) with formula d.f. = n – 1 (n = volume of sample size) and applying t test. t test value was 3.5193 and according to British Medical Journal tables (27) is statistically significant.

DISCUSSIONS

Recent literature data has proven that FeNO is a relevant clinical marker in various aspects of asthma: is a predictor of possible asthma development in patients with persistent rhinitis or in children with persistent respiratory features and is useful in monitoring patients treated with omalizumab, etc. (12).

FeNO measurement seems to have an important role in pediatric patient evaluation for an asthma

	A	B	C	D
1	ACT	FENO	gender	
2	17	67		
3	22	3		
4	24	3	M	
5	22	15	F	
6	23	6	M	
7	20	16	M	
8	23	29	M	
9	24	22	M	
10	25	3	M	
11	24	6	M	
12	23	6	M	
13	24	8	M	
14	23	8	M	
15	21	3	M	
16	25	4	M	
17	24	6	M	
18	21	38	M	
19	21	0	M	after 5 days of iv Dexamethasone
20	25	2	M	
21	20	8	M	after 24 hours of oral CS (35mg Prednisone)
22		-0.62863	M	r- Pearson correlation coefficient
23	2.0641	16.1091	M	standard deviation
24	0.461	3.597		standard error of deviation
25	19			degrees of freedom
26	3.5193			t test
27	0.01>p>0.001			p
28				

FIGURE 5. *Statistic data in Excel*

suspicion and in management of children with proven asthma (9). FeNO is used in assessment of one of the most frequent chronic or recurrent symptom in children presented as outpatients: chronic cough (10, 31).

Although some authors consider important that FeNO measurement has to be performed both before and after PFT's (11), in present study FeNO was measured before spirometry. None of the patients had exacerbation of asthma during evaluation.

Results of our study were correlated with other cohorts of pediatric patients:

1. A study performed in Mexican children (161 children aged 6-18 years) has proven that FeNO below 20ppb is associated with a higher ACT score than in children with FeNO above 20ppb. These later children have low ACT score and low FEV1% (20).

2. Another study done in Spain is documenting a good correlation between ACT score and FeNO value, but emphasizes that normal ACT score can be present in children with high FeNO values (>35ppb). It is possible that a subclinical inflammation ("poor-perceivers") or an exacerbation in the near future to be documented in these cases (21).

3. Two pediatric studies are documenting the importance of FeNO measurement and correlation between FeNO and level of asthma control (7, 8).

There are also negative studies which conclude that no link can be documented between ACT and FeNO levels (Margherita Neri in a study from Italy) (22).

Young female adult, 26 years old medical resident, was presented in ED for respiratory distress and cough in the last 3 days (nocturnal worsening), with no controller treatment since age of 10 (because partial remission of symptoms). She had ACT score 20, FeNO 24 ppb, and PEF 290L/min (75% predicted). Bronchospasm was reversible on salbutamol (after 3 puffs of Ventolin, PEF 390 L/min = 101% predicted). After 4 weeks of correct treatment ACT score rose at 24 and PFT's normalized: PEF 390 L/min (101% predicted).

Main study limitation is the relative low number of included patients. In order to increase the power of these findings it is recommended to include between 50 and 100 patients (28).

CONCLUSION

1. FeNO measurement is a simple, rapid and non-invasive method and is easily accepted by children.

2. FeNO value is correlated with ACT score, in a linear and negative way ($r = -0.6286$), statistically significant.

3. FeNO could be used in children for asthma diagnosis and monitoring: in diagnostic approach of inconclusive cases of children with recurrent wheezing or chronic cough, or in compliance estimation, etc.

4. Patients with a low ACT score (< 19) and a normal FeNO level will benefit of a different approach than a further increase of ICS if they are already on inhaled steroids. These children have non-eosinophilic inflammation and will be probably non-responders.

5. Simple algorithms that include FeNO and ACT could improve diagnosis, treatment and monitoring of asthmatic children.

REFERENCES

1. **Forstermann U., Sessa W.C.** Nitric oxide synthases: regulation and function. *Eur Heart J* 2012; 33(7):829-37, 837a-837d.
2. **Lowry J.L., Brovcokych V., Zhang Y., et al.** Endothelial Nitric-oxide Synthase Activation Generates an Inducible Nitric-oxide Synthase-like Output of Nitric Oxide in Inflamed Endothelium. *The Journal of Biological Chemistry* 2013; 288, 4174-93.
3. **Pijnenburg M.W.H., De Jongste J.C.** Exhaled nitric oxide in childhood asthma: a review. *Clinical & Experimental Allergy* 2008; 38(2), 246-59.
4. **Kharitonov S.A., Chung K.F., Evans D., O'Connor B.J., Barnes P.J.** Increased exhaled nitric oxide in asthma is mainly derived from the lower respiratory tract. *Am J Respir Crit Care Med.* 1996; 153(6 Pt 1):1773-80.
5. **Douwes J., Gibson P., Pekkanen J., Pearce N.** Non-eosinophilic asthma: importance and possible mechanisms, *Thorax* 2002; 57:643-8.
6. **McGrath K.W., Icitovic N., Boushey H.A., et al.** Alarge subgroup of mild-to-moderate asthma is persistently noneosinophilic, *Am J Respir Crit Care Med.* 2012; 185(6):612-9.
7. **Hahn Y.S.** Measurements of fractional exhaled nitric oxide in pediatric asthma, *Korean J Pediatr.* 2013; 56(10):424-430.
8. **Xiang L., Fu Y.N., Li Z., Ren Y.X., Rao X.C.** Value of fractional nitric oxide concentration in exhaled breath in assessing level of asthma control in children, Zhongguo Dang Dai Er Ke Za Zhi. 2013; 15(1):29-32.
9. **Mahr T.A., Malka J., Spahn J.D.** Inflammometry in pediatric asthma: a review of fractional exhaled nitric oxide in clinical practice, *Allergy Asthma Proc.* 2013; 34(3):210-9.
10. **Kelekçi S., Sen V., Yolbas I., Uluca Ü., Tan I., Gürkan M.F.** FeNO levels in children with asthma and other diseases of the lung. *Eur Rev Med Pharmacol Sci.* 2013; 17(22):3078-82.

11. **Tomasz G., Pawel M., Joanna J., Wlodzimierz S., Rafal S., et al.** The interpretation of exhaled nitric oxide values in children with asthma depends on the degree of bronchoconstriction and the levels of asthma severity, *Respir Care*. 2013; (Epub ahead of print).
12. **Ricciardolo F.L.** Revisiting the role of exhaled nitric oxide in asthma, *Curr Opin Pulm Med.* 2014; 20(1):53-9.
13. **Baraldi E., Azzolin N.M., Zanconato S., Dario C., Zacchello F.** Corticosteroids decrease exhaled nitric oxide in children with acute asthma. *J. Pediatr.* 1997; 131:381–5.
14. **Barnes P.J., Dweik R.A., Gelb A.F., Gibson S.C., et al.** Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest.* 2010; 138(3):682-92.
15. **de Winter-de Groot K.M., Van der Ent C.K.** Nitric oxide in cystic fibrosis. *Journal of Cystic Fibrosis* 2005; 4 Suppl 2: 25-9.
16. **Hatziagorou E., Tsanakas J.** Assessment of airway inflammation with exhaled NO measurement, *Hippokratia.* 2007; 11(2): 51–62.
17. An Official ATS Clinical Practice Guideline:Interpretation of Exhaled Nitric Oxide Levels (FeNO)for Clinical Applications,May 2011
18. *** http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htmaccesat in 25 februarie 2014
19. *** http://www.aaaai.org/about-the-aaaai/newsroom/asthma-statistics.aspx accesat în 25 februarie 2014
20. **Soto-Ramos M., Castro-Rodríguez J.A., Hinojos-Gallardo L.C., Hernández-Saldaña R., et al.** Fractional exhaled nitric oxide has a good correlation with asthma control and lung function in latino children with asthma, *J Asthma* 2013; 50(6):590-4.
21. **Javier Alvarez-Gutiérrez F., Medina-Gallardo J.F., Pérez-Navarro P., Martín-Villasclaras J.J., et al.** Relationship of the Asthma Control Test (ACT) with Lung Function, Levels of Exhaled Nitric Oxide and Control According to the Global Initiative for Asthma (GINA). *Arch Bronconeumol.* 2010; 46:370-7
22. **Neri M.** Does the asthma control test reflect inflammation? Multidisciplinary Respiratory Medicine 2011, 6:270-1
23. **Price D.R., Burden A., von Ziegenweidt J., Gould S., et al**. Using fractional exhaled nitric oxyde (FENO) to diagnose steroid-responsive disease and guide asthma management in routine care, *Clinical and Translational Allergy* 2013; 3(1):37
24. **Bora M., Alppaydin A.O., Yorgangioglu A., Akkas G. et al.** Does asthma control as assessed by the asthma control test reflect airway inflammation? *Multidiscip Respir Med.* 2011; 6(5):291-8.
25. **Waibel V., Ulmer H., Horak E.** Assessing asthma control: symptom scores, GINA levels of asthma control, lung function, and exhaled nitric oxide. *Pediatr Pulmonol.* 2012; 47(2):113-8.
26. **Yavuz S.T., Civelek E., Sahiner U.M., Buyuktiryaki A.B. et al.** Identifying uncontrolled asthma in children with the childhood asthma control test or exhaled nitric oxide measurement. *Ann Allergy Asthma Immunol.* 2012; 109(1):36-40.
27. *** http://www.bmj.com/about-bmj/resources-readers/publications/statistics-square-one/11-correlation-and-regression accesat in 25 februarie 2014.
28. **Haussermann S., Kappeler D., Schmidt A., Siekmeier R.** Fractional exhaled nitric oxide in clinical trials: an overview. *Adv Exp Med Biol.* 2013; 788:237-45.
29. **Zairina E., Stewart K., Abramson M.J., George J.** The effectiveness of non-pharmacological healthcare interventions for asthma management during pregnancy: a systematic review. *BMC Pulm Med.* 2014; 14(1):46. (Epub ahead of print)
30. **Stonham C.** Using FeNO in the diagnosis and management of asthma. *Br J Nurs* 2014; 23(5):266-x
31. **Poulose V.** Usefulness of FeNO in the Diagnosis of Chronic Cough. *Chest.* 2014;145(3 Suppl):567A
32. *** http://www.ncbi.nlm.nih.gov/pubmed/?term=nitric+oxide+AND+child accesat in 21 martie 2014.