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RESEARCH ARTICLE

# IS THERE AN IDEAL BIOMARKER FOR PEDIATRIC ASTHMA?

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## INTRODUCTION

The declared purpose of this article is to provide all the instruments, in terms of definitions in order to reveal the role of biomarkers in pediatric asthma.

The term of biomarker was first used in 1989 [1], the concept referring to a biological marker.[2]

Hulka defines biomarkers as "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids", but the official definition is provided by the National Institutes of Health. According to this a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." (Biomarkers Definitions Working Group, Pharmacol Ther, 2001) In order to be in biomarker, this indicator must possess certain characteristics: accurate, reliable, reproducible, standardized to have a high sensitivity and specificity, easily interpretable, to be acceptable to the patient and have clinical impact. (Vasan R, S)

The ideal biomarker should reunite the following criteria:

- clear relationship with the studied disease or pathophysiological condition;
- high reproducibility and reliability;
- reduced or no diurnal variability;
- specific and sensitive for the studied disease;
- simple method of identification and acceptable to the patients;
- low-cost, so the application in a broader population is advantageous. (Lesko LJ, Atkinson AJ, 2001)

The study of biomarkers involves several steps, as: identification of biomarkers, verification and validation, preclinical implementation and, in a later stage, clinical implementation.

**Biomarkers of inflammation in asthma**

***Sources of biomarkers to assess inflammation in asthma***

Biomarkers can be identified both in the respiratory tract and lung, and in extrapulmonary sources, such as blood and urine.

The sources for the identification of biomarkers for inflammation in asthma are:

***Biopsy***

The biopsy fragments are difficult to be taken generally because of the low acceptance of the patients, therefore they are more difficult to obtain from the pediatric population. Thus, biopsy data are practically non-existent in children with mild to moderate asthma, so early inflammatory changes of asthmatic pediatric population could not be documented. [3]

***Bronchoscopy and biopsy***

Although it is considered the "gold standard" in assessing inflammation of the asthmatic airways has limited value in assessing pediatric asthma correlated with it's invasiveness. [4,5]

Except for non-tumoral pathology, asthma is the most common indication for performing bronchoscopy with biopsy in order to evaluate the inflammation and airway remodeling .[6]

Most restraint are correlated with child's safety while performing bronchos copy, which makes this method not acceptable for patients. Adding further the investigatory biopsyaddsnorisk to the maneuver.[6]

***Bronchoalveolar lavage fluid- BAL***

Bronchoalveolar lavage fluid is obtained by a minimally invasive method involving collecting samples containing free cells and acellular material from the surface of distal respiratory epithelium. Accurately recovered cells reflect the intensity of interstitial inflammation, therefore BAL is used to define immunological mechanisms. Represents the last line method for assessing asthma in children. [7]

***Sputum***

Induction of sputum production is possible for children over 6 years old, this noninvasive technique is considered relatively safe. It seems to be a reliable method for the assessment of airway inflammation during asthma exacerbation.[4,8]

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Evaluation of sputum allows direct evaluation of bronchial inflammation, brings data on early inflammatory response and allows the identification of different phenotypes of asthma, but the specimen preparation techniques, however, need to be refine. [4.8]

***Exhaled breath condensate- EBC***

The condensate can be evaluated for various respiratory inflammatory markers - citokines- IL4, IFNγ, LT and markers of oxidative stress. [4.9]

The source of breath condensate remains controversial, as some authors consider its source being the large airways, others however, consider its origin as broncho-alveolar.

The measurement is based on the assumption that Barnes and Kharitonov made "nonvolatile aerosol particles reflect exhaled bronchoalveolar extracellular fluid composition."

Exaled breath condensate is a valuable and very promising source of biomarkers in respiratory diseases, in general, and asthma, in particular. EBC is not a biomarker by itself, but an amalgam of biomarkers and potential biomar kers, which makes it the equivalent of blood, urine, saliva or tears.[10]

Biomarkers of respiratory condensate exhibit great variability, these data providing possibilities for individualized therapies. [11]

Exaled breath condensate has the advantage of being completely noninvasive, relatively easy to obtain, including from ventilated pediatric patients, and it is a method able to evaluate several parameters simultaneously. Nonvolatile constituents and the water soluble constituents arouse a particular interest. [9,11,12,13]

Blood is evaluated in pediatric asthma especially in terms of eosinophilia, eosinophilic cationic protein and IgE. More and more biomarkers are identified serving to the asthmatic child. [4]

Urine, as well as blood, is of limited value in providing airway inflammation data. The most evaluated biomarkers in urine are eosinophilic protein X, resulting from eosinophil activation of and LTE4. [4]

Recent study from Mattarucchi et colab. show that the reduction of the urinary content of urocanic acid methyl-imidazoleacetic acid can be correlated with their newly discovered roles in inflammatory diseases. Further studies are required, however, to confirm these data. [14]

***Types of biomarkers used in asthmatic inflammation***

The asthmatic inflammation involves resident cells of the lungs and inflammatory cells recruited to the site of inflammation under the action of the molecules gathered at this level. The cells involved in asthmatic inflammation are: epithelial cells, dendritic cells, mast cells, eosinophils, natural killer cells, neutrophils, basophils, platelets and lymphocytes. These cells produce proinflamatory cytokines such - IL1α, IL1β, IL 6, IL8, IL11, IL17, IL22, TNF, TNFβ, IFNγ- and inflammation mediators such as histamine , bradykinin, proteases, leukotrienes, prostaglandins, eotaxin, eosinophilic cationic protein, basic major protein, adhesion molecules, products of oxidative stress, and these are just a few of the actors involved in the production of asthmatic inflammation.

**Cellular biomarkers**

The presence of inflammatory cells in the asthmatic lung can be documented especially in biopsy specimens, and in induced sputum and bronchoalveolar lavage fluid. Although there are studies proving the safety of bronchial biopsies in pediatric patients, the use of the method is still limited because of its invasive nature and acceptability for pacient.[5,6]

On the fragments collected and examined with electronic microscopy have been demonstrated structural changes and the presence of inflammatory cells, represented mainly by lymphocytes, mast cell degranulation at various stages, macrophage, and eosinophilic and neutrophilic infiltration.[4]

Most studies were directed toward evaluating eosinophilic infiltration and its repercussions on the development of asthma. Thus:

- in asthma, especially atopic asthma, there is an increase in the number of airway as well as serum eosinophils [4];
- the number of eosinophils is elevated in sputum , bronchoalveolar lavage fluid, serum and bone marrow; [15,16]
- eosinophilia levels correlate with the severity of the disease; [15, 17]
- there are studies showing that asthma typical structural changes develop even in the absence of eosinophilic infiltrate, suggesting the involvement of other mechanisms; [18]
- study of asthmatic children with corticotherapy (inhaled or oral) showed significant increase in sputum eosinophilia compared with controls; [4]
- eosinophilia is reduced also by leukotriene inhibitor therapy; [4]
- sputum eosinophilia is predictive for the response to inhaled corticosteroid therapy,the dose of CSI can be adjusted in order to maintaine sputum eosinophilia below 2%. [17,19, 20]
- there is controversy in the literature regarding the correlation between eosinophilia, asthma control and exacerbations. Therefore many studies attest that anti-inflammatory therapy based on reducing the number of eosinophils in sputum shorten exacerbations, and combined therapy of cortisone and an anti-IL5-mepolizumab, brings the number of eosinophils in normal ranges, [21] other studies claim that the introduction of eosinophilia in the asthma control algorithm management has not improved its control nor significantly reduced the number of exacerbations.[22]

Poliomorfonuclear infiltrate was found in bronchoalveolar lavage fluid, correlating with the severity of asthma symptoms. PMN inflammation correlates better with viral-induced wheezing, rather than asthma.[4]

Patients with severe refractory asthma sometimes demonstrate increased number of neutrophils in the airways. [21]

**Proteic Biomarkers**

"OMICS biology " is able to identify associations between genes - proteins - disease using new genomics and proteomics techniques. A series of pathophysiological changes encountered in asthma are attributed to proteins associated with transcriptional pathways, production of cytokines, chemokines and inflammatory mediators and cellular proliferation or apoptosis [23,24]

Many of these proteins are subject of studies to identify those proteins or combinations of proteins that can become biomarkers of asthma.

***Cytokines***

Cytokines are soluble molecules, [25] mediators of intercellular communication, with numerous effects. Cytokines classification can be made according to their molecular structure or function, as follows:

- cytokines involved in the early inflammatory response
- recruiter group include chemokines- group responsible for recruitment of various types of leukocytes to sites of inflammation.

Sources of cytokines involved in the pathogenesis of asthma are cells both structural and recruited, their central role being to perpetuate the inflammatory process. Almost every cell is capable of releasing cytokines in certain circumstances, each cytokine being capable of inducing the release of other cytokines, to form a complex and interconnected network .[26]

**Corelations between cytokines- IL and asthma**

- based on genetic polymorphism of IL 4 receptor patients can be divided into subgroups of patients that respond to the treatment with antagonists of these receptors; [27]
- IL 6 levels are increased in serum, bronchoalveolar lavage fluid and sputum in asthmatic patients, fact correlated high levels of IL 13; [28,29]
- IL 17 expression is increased in sputum of asthmatic patients, unaffected by cortisone therapy and is an independent risk factor for the severe asthma; [30.31]
- IL-18 plays an important role in the pathogenesis of asthma, according to a recent study, some other studies associate it with the etiology and progression of asthma. [32]

Chemokines are small molecular weight proteic molecules responsible for the chemotactic effect along the cell membrane, resulting different types of cell infiltration at the inflammation site. [33,34,35]

Chemokines are active molecules even at small concentrations.[34]

Depending on the position of the first two cysteine residues, chemokines were divided into four families: CC- of 27 described in mammals, CXC- 17 members described in mammals, C - α and β limphotactin, CX3C- fractalin / neurotactin; [34]

More than 50 chemokines were discovered in humans and over 20 receptors.

The most studied in correlation with asthma is eotaxin.[36,37]

Eotaxin was discovered in 1993 after an experiment in which a non-sensitized guinea pig was injected intradermally with bronchoalveolar lavage fluid originated from a guinea pig sensitized to allergens, the result being eosinophils recruitment . [38]

It is a small proteic molecule with 74 amino acids with three forms derived from macrophages, epithelial cells, endothelium, fibroblasts. It may be, also, produced by mobile cells and may be identified in bronchoalveolar lavage fluid. [39]

Its release is dependent on IL4, IL13, αTNF.[39]

Eotaxin is responsible for Th2 lymphocite chemotaxis, being considered the most powerful recruiter of eosinophils. [39, 40]

These three forms are secreted in different stages of the inflammatory response:

- eotaxin 1 is constitutional, can be found both in healthy volunteers and in patients with allergies, in which is responsible for the early stages of allergic response; [39]
- eotaxin 2, 3 appear after allergen stimulation and are responsible for persistent eosinophilia in late asthmatic response.[39]

Berkman *et al*. showed that only expression of eotaxin 3 at 24 hours after allergen exposure is able to distinguish between asthmatic and healthy subjects. [30]

Eotaxin levels are elevated in asthma, especially in severe asthma, and can contribute to asthma severity and control. Antagonizing CCR3 receptor may limit the toxic effects eosinophil- associated in asthmatic lung. [38]

***Tachykinins***

The most relevant are substance P, neurokinin A and neurokinin B which are polypeptides belonging to the class of neuropeptides. Are found mainly in the brain where it exerts stimulatory effects. They are also involved in inflammation known as "neurogenic inflammation", as well as in adaptive immunity. [41]
These peptide molecules act mainly via three specific receptors: NK1, NK2, NK3. There is evidence that tachykinins may modulate immune responses, regulating the production of IL 1,6,8 and TNFα. [41]

These three types of receptors may represent targets for new therapies .[42]

There are studies proving weak or absent effects of tachykinin receptor antagonists on the inflammation but the effects are more relevant when bronchial hyperreactivity is concerned. [42]

Tachykinins involvement in the pathogenesis of asthma and the right combination in which they can be used as valuable biomarkers remains to be studied.

*Eosinophilic cationic protein- ECP*

ECP produced by activated eosinophils is responsible for ciliary dysfunction, bronchial epithelium damage and cell denudation, and airway hyperreactivity .[43]

Eosinophilic cationic protein has been extensively studied in relation to asthma and it can be identified in sputum, bronchoalveolar lavage fluid, saliva and serum .[45]

Serum ECP levels are increased in asthma correlated with inflammation and asthma severity, with no correlation with bronchial hyperreactivity, therefore it is possible to assess the compliance to therapy and level of severity. [44.45] ECP is a diagnostic test, but may be useful as a marker of the severity. Its levels can be affected by circadian rhythm, age, smoking, seasonal variations, especially related to allergic reactions. [45]

*Galectin 10* Galectins are proteic molecules belonging to the lectin family. Until now there were identified at least 12 galectins widely distributed in the body. The most studied are galectin 1 and galectin 3. [46]

Galectin 10 (Charcot-Leyden Crystal) is specific for eosinophils and basophils, being a unique marker of peripheral eosinophilic inflammation. Recent studies highlight its regulatory roles on T cells, the ability to damage the respiratory epithelium and increase vascular permeability, thereby having the potential to be used as a biomarker for asthma. [46,47, 48]

***YKL-40 or Chitinase 3-like protein 1***

YKL -40 is a is a glycoproteic molecule of chitinase family, a molecule with a recent discovered potential as a bioamarker correlated with asthma. The molecule is inactive as enzyme.

***YKL-40 is an inflammatory biomarker***

- high levels in serum and also in bronchoalveolar lavage fluid of asthmatic patients; [49.51]
- high levels correlate with allergic inflammation; [49]
- correlates with the severity of the asthma disease; [49.51]
- correlates with fibrosis and bronchial remodeling; [49.51]
- promotes proliferation of smooth muscle cells of the asthmatic airways; [52]
- high levels in sputum reflect airway obstruction; [53]
- YKL-40 determination on admission correlated with overall mortality, regardless of diagnosis, and can be used as a biomarker of any acute distress. [49]
- Recent studies in adult demonstrate that YKL-40 levels correlated with sputum neutrophilia. [51]

**Lipid biomarkers**

*Platelet-**activating** factor* – ***PAF-*** is a phospholipid with multiple leukocyte functions, platelet aggregation and degranulation, inflammation and anaphylaxis.

In asthma, PAF is produced by the cells involved in inflammation, mast cells, eosinophils, neutrophils and it is responsabil for eosinophil recruitment, bronchial hyperreactivity and broncho constriction.[33]

***Arachidonic acid metabolites***

Prostaglandins and leukotrienes are key mediators of bronchial inflammation and remodeling. Arachidonic acid results from the degradation of cell membranes lipids by two enzymes-cyclooxygenase and lipoxygenase via two metabolic pathways leading to leukotrienes, prostaglandins and thromboxane. [31]

Prostaglandins play an important role in asthmatic inflammation. Prostaglandin E2 exerts its effects through four G protein-coupled receptors, receptors differently represented on the different cells: B and T cells, neutrophils, dendritic cells, modulating the immune responses. These effects are proinflammatory and anti-inflammatory in the same time. [31]

*Aggarval et.al*, 2010 demonstrated that patients with allergic eosinophilic asthma have high PGE2 levels in induced sputum.[13]

Prostaglandin D2 stimulates the production of proinflammatory IL - IL 4,5,13, the polarization of T lymphocite to Th2, and is also a Th2 recruitor. [4,31,33]

Leukotrienes are potent mediators of inflammation in asthma: LT C4 is found in high amounts in the plasma of children with severe asthma, LTE4 is increased during asthmatic exacerbations.[4.33]

A study recent- Sampson et. colab. attest a up-regulation phenomenon of leukotriene synthesis in non-asthmatics allergic patients compared to the allergic asthmatics.[54]

Leukotriene E4 can be measured noninvasively in the urine, as a measure of total capital of CysLT of the body. This capital changes correlated with changes in body CysLT in different environments, including airways. Urinary LTE4 level is a sensitive marker for assessing exposure to triggers. This biomarker may not be accurate for children due to reduced capacity to concentrate urine and reduced levels of creatinine. [4]

***Biomarkers correlated with oxidative stress***

The lung is the only organ exposed to oxidants coming from both the external and internal environment, which are an

important source of lung injury. Lung has a well organized system of antioxidants. [3]

Oxidative stress is due to an imbalance between oxidants and antioxidants and is present in asthma. [3.55]Pulmonary oxidants are:

- reactive oxygen species - SRO - superoxide, hydrogen peroxide, hydroxyl radicals; [55]
- reactive nitrogen species resulting the nitric oxide.[3]

Reactive oxygen species are toxic molecules with multiple levels of action: alteration of DNA bases, protein, peroxidation of lipids. They correlate with asthma inflammation.[55]

***In a recent study, in 2012, Trischler et.colab. first certify that***

- hydrogen peroxide in respiratory condensate of asthmatic children was significantly higher in the airways fraction compared with the alveolar fraction.
- for the children over 12 years of age only H2O2 from alveolar fraction correlates with asthma control;
- there was no correlation between H2O2 fractions and the type of inhaled corticosteroid used;
- there is no positive correlation between H2O2 and phenol, regardless of the fraction considered; [56]

However, expired fraction of H2O2 can be the marker of the alveolar involvement in asthmatics, but other further investigation in needed. [56]

- Increased oxidative stress in asthma is reflected by:
- high serum levels of malon-dialdehyde;
- presence of protein carbonyls in the blood and bronchoalveolar lavage fluid;
- increased the oxidized glutathione in bronchoalveolar lavage fluid;
- presence of H2O2, CO, 8-isoprostane in broncho-alveolar condensate; [55.57]
- Corradi *et al*. showed high levels of aldehydes and lower glutathione in the exaled breath condensate during exacerbations, and reduced levels of aldehydes after using of inhaled corticosteroids.[4]

Nitric oxide- NO , the "star" molecule since 20 years ago, is intensively studied and keeping actual in studies about asthma:

- was discovered in 1987 and named endothelium-derived relaxing factor;
- in 1992 was named "molecule of the year" the Science journal;
- in 1998 Furchgott, Ignarro and Murad were awarded the Nobel Prize for their contributions to the discovery of NO and its signals. [58]

Nitric oxide is generated by the action of inducible nitric oxide synthase (isoform 2) present at the bronchial epithelium, mast cells, basophils and eosinophils. [3.58]

Nitric oxide can be measured as a exhaled fraction- eNO- that correlate with asthma and other markers identified in asthma.

A recent study shows that phenol is useful for early diagnosis of pediatric asthma, especially when the diagnosis is notclar.[58]NOconstitute ausefulmarkere specially for the children without corticosteroid therapy versus those with persistent asthma controlled with in haled corticosteroids. eNO levels are significantly higher in children with intermittent asthma compared with those with moderate persistent asthma treated with inhaled corticosteroids. [4]

Management therapy based on Fe NO values does not correlate with better control of asthma, according to a recent study, so its use in current practice is not justifiable.[59]

**Other markers and biomarkers associated with asthma**

**Vitamin D**

The involvement of vitamin D in respiratory pathology, immunity and asthma was recently discovered. Thus, it certifies the association of genes involved in the metabolism of vitamin D and certain features of asthma.

Vitamin D has been linked to lung and immune system development in utero. 1,25 dihydroxy-vitamin D3 can be generated in other tissues outside the kidney, and the VDR receptor is also expressed in the immune cells without being related to phospho-calcium homeostasis. [60,61,62]

**Low levels of vitamin D are associated with**

- Lung diseases, including viral and bacterial infections, asthma, chronic obstructive pulmonary disease, cancer; [61]
- In asthmatic lung there are correlations with modified pulmonary function, increased airway responsiveness, reduced response to corticosteroids; [63,64,65,66,67]
- Low levels of 25 hydroxy D3 are increasing severity of asthmatic exacerbations and reduce asthma control .[66]

Therefore, we can draw suggestive directions to be followed by additional therapy with vitamin D, which could improve multiple parameters of asthma severity and control. According to epidemiological data supplementation in pregnant women reduces the risk of asthma up to 40% for the children aged between 3 and 5 years. [60, 63]

Biomarkers and panels of biomarkers National Institute of Health brought together a group of experts to propose biomarkers that should be evaluated and standardized for the asthma assessment in the future.

**In this project, biomarkers were classified in:**

- "Core" biomarkers involving multialergen testing to define atopy;
- Additional biomarkers - total and sputum eosinophilia , FeNO, urinary LT, total and specific IgE;

- Developing biomarkers - "emerging" - sputum neutrophils , cortisol, imaging and data provided by science "OMICS" .[6]

Other authors have turned their attention to the determination of four proteic molecules involved in iron metabolism: α2 macroglobulin, haptoglobin, ceruloplasmin, hemopexin and concluded that iron metabolism and acute phase response may be involved in the pathogenesis of respiratory diseases.[68]

Proteins such as RELMα (FIZZ-1), calcyclin (S100A6), clear cell secretory protein 10 (CC10), ubiquitin and histone H4 were the subject of other studies to identify valuable biomarkers.[69]

Given the genetic and molecular heterogeneity of asthma, the identification of that perfect biomarker to provide comprehensive data on the disease seems unlikely . More likely it is to identify a set of markers able to constitute a clue for diagnostic, therapy and prognostic and able to identify those individuals who are at risk of developing asthma.

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