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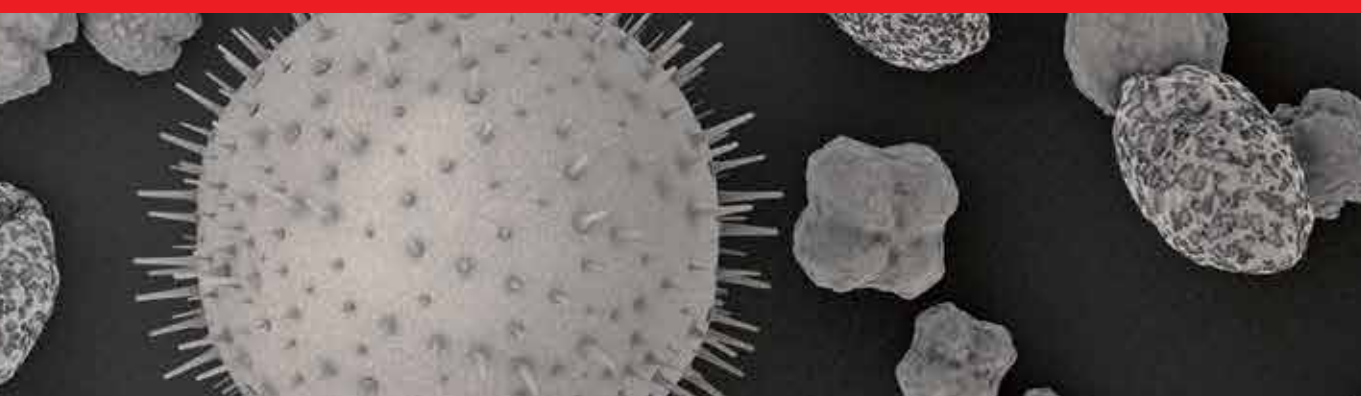
Asthma Diagnosis and Management

Approach Based on Phenotype and Endotype

Edited by Kuan-Hsiang Gary Huang and Chen Hsuan Sherry Tsai



ASTHMA DIAGNOSIS AND MANAGEMENT - APPROACH BASED ON PHENOTYPE AND ENDOTYPE

Edited by **Kuan-Hsiang Gary Huang** and **Chen Hsuan Sherry Tsai**

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Contributors

Alex Kleinjan, Jan Beute, Vincent Manganiello, Mirjana Turkalj, Sanela Domuz Vujnović, Adrijana Domuz, Jose Carlos Herrera Garcia, Ek I Arellano Montellano, Enrique Jaramillo Arellano, Drew Harris, Y. Michael Shim, Caitlin Welch, Morgan Soper (msw), Carlos D Serrano Reyes, Dolly Rojas Mejía, Diana Silva, Francisco Muñoz-López, So Ri Kim, Yong Chul Lee, Slobodanka Branko Petrović, Marcia Regina Piuvezam, Claudio Bezerra-Santos, Giciane Vieira, Laercia Karla Diega Paiva-Ferreira, Talissa Mozzini-Monteiro, David Skalický, Václav Koucký, Frantisek Lopot, Daniel Hadraba, Marina Otelea, Agripina Rascu

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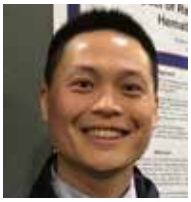
Meet the editors



Gary KH Huang, MD, PhD, MSc, is the director of Allergy, Asthma and Immunology at Albert Einstein Medical Center and assistant professor at Thomas Jefferson University Hospital, USA. A Rhodes Scholar, Gary completed his medical degree at the University of the Witwatersrand followed by MSc and DPhil at the University of Oxford. He then served residency and chief residency at Albert Einstein Medical Center and allergy and immunology fellowship at the University of Pennsylvania. His research has been published in leading journals including Nature Communications and Proceedings of the National Academy of Sciences, and his current research is supported by the American College of Allergy, Asthma and Immunology. As a physician scientist, Gary is interested to further personalized medicine in asthma.

Chen Hsuan Sherry Tsai, MD, PhD, is currently a medicine resident at Albert Einstein Medical Center, Philadelphia, USA. Sherry is an MBBCh medical graduate from the University of Witwatersrand in South Africa and a DPhil graduate from the University of Oxford in the UK. She worked as a postdoctoral fellow at Drexel University prior to her medicine residency in 2015. Dr. Tsai is a member of American College of Physicians (ACP) and is active in clinical publications.

Contents

Preface

Asthma is a severe and growing threat affecting both children and adults in both developing and developed world, currently affecting approximately 8% of US population. It is becoming increasingly recognized as a syndrome constituted by airway obstruction, airway hyperresponsiveness, and airway inflammation with different causes, associated risk factors, and underlying pathophysiology. The advances in basic and clinical research of asthma have accelerated over the past 20 years with increasing diagnostic tools, especially biomarkers, that led to specific characterization of individual patient's asthma pathophysiology, or disease "phenotype" and "endotype," which allowed precision medicine therapies, including new asthma biologics. Many biomarkers are also very useful in disease monitoring and prognostication. It is therefore fitting for us to compose this book to update the paradigm shifts in precision medicine of asthma diagnosis and management, driven by underlying phenotypes or endotypes.

Many individuals have made invaluable contributions to the making of this book, we thank each author and his/her colleagues for their insights and contributions. We are grateful to the Commissioning Editor, Ms. Danijela Vladika, and everyone at InTechOpen Publisher for the wonderful support in preparation of this book for publishing. Finally, we would like to dedicate and share this book to our parents and family, especially our beautiful daughter, Ping-Hwa Pierra Huang. We love her beyond words, and her intellectual curiosity inspired us to further our academic rigor; we hope to always serve as her role model and cherish her loveliness.

Chen Hsuan Sherry Tsai, MBBCh (Wits), DPhil (Oxon)
Albert Einstein Medical Center, USA

Kuan-Hsiang Gary Huang, MBBCh (Wits), DPhil (Oxon), MSc (Oxon)
Albert Einstein Medical Center, USA
Thomas Jefferson University Hospital, USA

Section 1

Advances in Epidemiology, Diagnostic and Basic Science of Asthma

Chapter 1

Noninvasive Biomarkers of Asthma

Mirjana Turkalj, Damir Erceg and
Iva Dumbović Dubravčić

Additional information is available at the end of the chapter

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Abstract

Asthma is a heterogeneous disease of the lower airways including various types of bronchial inflammation presenting with different phenotypes and endotypes. Therapeutic response of asthmatic phenotypes/endotypes can be predicted by the use of biomarkers of inflammation phenotyping, and in recent years, endotyping of asthmatics allows to predict who will best respond to anti-inflammatory treatment and optimize quality of life of asthmatics by reducing the risk of exacerbations. Based on noninvasive biomarkers of inflammations, several of them have been described that are useful in clinical practice. Some of the noninvasive biomarkers have a particularly important role in the diagnosis and treatment of asthmatics. Monitoring of noninvasive biomarkers, such as fraction of exhaled nitric oxide (FENO), cells in sputum, or biomarkers in exhaled breath condensate (EBC), two main inflammatory phenotypes have been described: eosinophilic phenotype and neutrophilic phenotype. In eosinophilic asthma, as the most prevalent inflammatory phenotype, asthmatics have more than 3% eosinophils in the sputum, elevated levels of FENO, and elevated leukotriene's cytokine levels in EBC. The most extensively studied biomarkers in asthma are TH2 or more generally T2-related asthmatic endotype. Their clinical benefit might be used to phenotype/endotype features of the underlying type of inflammation and selection of asthmatics, particularly with severe or difficult-to-treat asthma, which most likely will respond to additional biological therapy. In this chapter, we summarize the noninvasive biomarkers available for the management of asthmatics.

Keywords: asthma, biomarker, inflammation, phenotype, endotype

1. Introduction

Asthma is a heterogeneous disease which includes a spectrum of different subtypes with different inflammation patterns responding differently to different treatments. The most

recently updated GINA guidelines address these issues emphasizing the importance of standardized diagnosis and appropriate treatment strategies according to asthma phenotype and/or endotype [1]. Generally, biomarkers or physiological measures that precisely and conclusively define phenotypes and asthma endotypes are missing or are insufficient. Several biomarkers have been described in asthma, but most of them including noninvasive biomarkers are not commonly available or still need external validation [2]. Many of the potential noninvasive biomarkers will be described in this chapter. Normal ranges and validation need to be established for most of them, and stability over time must be examined in longitudinal studies. The new research is needed about the effects of asthma therapy on biomarker measurements, especially for biomarkers which are proposed to guide different treatments, like therapy with biologics [3]. Finally, and most importantly, the new biomarkers, especially noninvasive, need to be easily sampled and interpreted at the point of care in order to provide and improve the diagnosis and treatment of different asthma subtypes, especially those which are more severe and therapy resistant. The challenge is how to identify "high-quality" biomarkers which have high accuracy and robustness that could predict clinical outcomes and therapy response which is of essential in the application of the concept of precision medicine.

2. Fraction of exhaled nitric oxide (FENO)

Fraction of exhaled nitric oxide (FENO) (or fractional exhaled NO) is currently the most widely used biomarker in the exhaled breath, and it is often increased in asthma, even in mild and asymptomatic condition [4]. Fractional exhaled nitric oxide or the modeling of NO dynamics of the lung can give more information than a single FENO value. The synthesis of NO is mediated by constitutive (endothelial NOS or neuronal NOS) and inducible NO synthase (iNOS). Its production is due to oxidation of L-arginine to L-citrulline. iNOS is the only isoform correlated with exhaled nitric oxide, and FENO has been considered as a marker of eosinophilic inflammation involving small airways [5]. FENO was found to be strongly reduced by treatment with inhaled corticosteroids (ICS) [6]. In a general population of asthmatics, it was found that the FENO threshold that best identified a sputum eosinophil count ≥3% in patients receiving high dose of ICS was 27 ppb [7]. In a recent paper, it was shown that, in severe asthma, FENO, had a lower accuracy than blood eosinophils to identify eosinophilic asthma [8], but increased FENO levels have been associated with a good response to ICS [6], oral corticosteroids, anti-IgE [9], and anti-IL-4 and anti-IL-13 [10, 11]. FENO is established as a marker of inflammation in asthma, but more than 20 years of research have shown that it works in certain asthma endotypes (TH2) [12]. Therefore, there is an increasing need for useful biomarkers with predictive and prognostic value for the progression of the disease in asthmatic patients and their link with clinical treatments.

3. Exhaled breath condensate (EBC)

Exhaled breath condensate (EBC) is the product of cooling and condensation of the exhaled aerosol, collected by tidal breathing during 10–30 minutes into a specially designed cooling

device [13]. It represents a potentially very useful method for noninvasive diagnosis of asthma and other pulmonary diseases. EBC consists of three major components, first being distilled water that comes from condensed gas phase of the exhalate. The second component are nonvolatile particles or droplets of different sizes that are aerosolized from the airway lining fluid (ALF), and final components are water-soluble volatiles that are exhaled and absorbed into the condensing breath [14]. Considering the origin of EBC, a large number of inflammation, oxidative stress, nitrosative stress biomarkers, or airway acidification indicators such as pH, adenosine, ammonia, free radicals, hydrogen peroxide, isoprostanes, leukotrienes, prostanoids, nitrogen oxides, peptides, and cytokines can be detected in EBC and have been studied last 20 years [15, 16]. These biomarkers can reflect the underlying state of lower airways as well as lung inflammation and can be altered in patients with asthma.

The collection procedure and requirements for the EBC collection devices as well as the storage and processing are still not standardized and validated due to many factors that influence the final outcome [15]. The final product of the collection is influenced by not only patient factors fluid and food intake timing, concurrent medication or drug intake, age, sex, weight, height, and disease but also external factors as room temperature, collection temperature, and device materials [15]. The volatiles and the nonvolatile particles of the EBC are highly diluted so the detection and analytics of the EBC are challenging tasks, furthermore due to the fact that there is no generally accepted dilution marker detected yet [16, 17].

4. Exhaled breath temperature (EBT)

Exhaled breath temperature (EBT) is a noninvasive method for detecting and monitoring pathological processes based on inflammation in bronchial lumen. According to the fact that heat is one of the cardinal signs of inflammation, the measurement of EBT was developed as a marker of airway inflammation and therefore used in the study of inflammatory respiratory diseases. The use of EBT devices is particularly attractive in patients with asthma who largely exhibit significantly higher EBT values compared with healthy subjects; these patients are therefore encouraged to use these exhaled thermometers in clinical practice for the maintenance of asthma control and in therapeutic management. In the currently available literature, there are almost 200 articles on the use of EBT in asthma and other respiratory diseases. Only few of these studies have assessed EBT measurements, and one recent study provides reliable reference values of EBT in healthy subjects. Despite the potential of EBT, it has not yet reached the clinical setting, partly because of a lack of standardization and validation of the method. However, a recent study deals with these obstacles. There are three groups of external temperatures influenced by EBT in different ways [18]. The first group considered the cases with external temperature ≤ 23°C In this case, the average EBT was 28.268 ± 2.872°C The second group considered cases measured with an external temperature of 23–28°C. In this case, EBT was 30.949 ± 2.511°C. The third group showed that if the test is performed with an external temperature > 28°C, the EBT was 32.558 ± 1.805°C. Authors did not report any influence by other variables, such as weight, height, blood oxygen saturation, lung function, area of residence, work, blood pressure, and axillary temperature, on EBT. Their findings are consistent with data from other authors [19]. There are several potential advantages of EBT

measurements: very easy for patients and requires only a few minutes; it is completely noninvasive and is therefore also suitable for children and patients with severe disease. The device is well accepted by patients and ethics committee, it is inexpensive, and it does not affect the underlying airway disease [20].

5. Electronic nose (e-Nose)

Exhaled breath contains thousands of volatile organic compounds (VOCs) in gaseous form that reflect the metabolic process occurring in the host, which may be used as markers of inflammation in the lung or systemically [21]. e-Nose is a portable device, which allows noninvasive, quick, and real-time pattern analysis of VOC spectra. Current e-Nose devices generally consist of an array of chemical sensors that specifically identify VOC mixture. Actually, e-Nose is a system of artificial sensor with chemical sensors that consists of an array for a qualitative and/or quantitative detection and description of VOC profiles or breath prints. Due to poor specificity to individual volatiles, chemical sensor arrays are not generally suitable for identifying single volatiles in complex mixtures of breath. Combining technologies, the high sensitivity of chemical sensor arrays with the high specificity of gas chromatography-mass spectrometry (GC-MS), which could mimic the performance of the natural olfactory system in e-Nose, can be used for identifying breath volatiles, as potential new markers of inflammations in different asthmatic sub-phenotypes [22, 23]. However, e-Nose technology has limitations. The optimal technique for breath collection, sampling, and analysis of single-breath volatiles indicating that future methodological studies are required is unknown. Miniaturized devices based on nanotechnology with micro- or nano-arrays are seen as a key in advancing a new e-Nose device.

Measurement of VOC by e-Nose can discriminate between patients with respiratory disease such as asthma and healthy controls. e-Nose breath prints are associated with the level of airway inflammation and might be useful in the assessment of asthma severity as well as can discriminate patients with fixed asthma from COPD patients with an 88% accuracy [24]. Longitudinal monitoring of exhaled metabolites measured by GC-MS and e-Nose can discriminate loss of asthma control [25]. The usefulness of measurement of VOC profiles by e-Nose in assessing asthma inflammatory phenotypes still needs to be confirmed.

6. Biomarkers in induced sputum

Induced sputum is a relatively noninvasive mode of airway sampling that provides an opportunity for analysis of cellular components and infective agents, including bacteria and viruses, together with fluid-phase constituents [26]. There are several standardized manuals that are available and help to educate health professionals how to perform the technique to the highest standard [27]. The application of induced sputum in the assessment of airway pathology has grown rapidly, especially after 2002, when European Respiratory Society (ERS) published the recommendations for standardization of sputum induction and processing [28, 29]. That is a

key component to provide valuable information for clinical decision-making. Sputum is collected after inhalations of hypertonic saline. Although relatively safe, induced sputum requires specialized training, equipment, and laboratory processing. Monitoring lung function during the induction procedure reduces the risk of excessive bronchoconstriction. Patient's active cooperation is needed for collection, making this technique unsuitable for some patients, especially for children below the age of 7 years. Induced sputum provides a rich source of soluble and cellular biomarkers. The sputum eosinophil percentage is a key biomarker which identifies patients who have eosinophilic and non-eosinophilic asthma phenotypes and correlates with severe exacerbations and AHR. Besides eosinophils, other sputum biomarkers are currently in research. Sputum neutrophils are often related to severe non-eosinophilic asthma with fixed airway obstruction. Soluble sputum biomarkers associated with asthma severity are IL-4, IL-5, IL-6, IL-12, IL-13, ECP, LT, TNF-α, CSF, TNF-α, and GM-CSF [30]. Biomarkers such as IL-8 and neurokinin A correlate with exacerbation, while procollagen synthesis peptides, tissue inhibitors of metalloproteinase, or THF-β have been associated with remodeling [31].

The widespread application of induced sputum in asthma proposed several disease phenotypes and defined which of these phenotypes respond to the current therapy. In neutrophilic asthma phenotype, the level of sputum mRNA expression of Toll-like receptors 2 and 4 as well as CD14 was high. Thus, this well-tolerated and safe method provides an additional tool to guide the clinical management of asthmatic patients [32]. To date induced sputum represents the only noninvasive measure of airway inflammation that has a clearly proven role in asthma management.

7. Biomarkers in urine of asthmatics

Urine is an easily accessible and noninvasive collectable biofluid containing many information about the current metabolic status of the body. Metabolic changes in the body of an asthmatic patient are reflected in the metabolite concentrations in urine, and the changes during asthma exacerbation can also be tracked well by urine metabolite analysis. Asthma, especially during exacerbation, causes a high level of oxidative stress due to the pulmonary reaction to exacerbation and resulting formation of reactive oxygen compounds that lead to cell damage. In children with asthma, the levels of LTE4 are increased in urine and are not altered under inhaled corticosteroid (ICS) therapy, but the 5-lipoxygenase inhibitors reduce the urinary LTE4 levels. Eosinophil protein X (EPX) is found in the urine of asthma patients, but the levels of the EPX fall within 3 months after anti-inflammatory therapy induction [33].

Prostaglandin D2 (PGD2) is released from mast cells, and it causes bronchoconstriction and vasodilatation in the airway. PGD2 is metabolized to 9α,11β-PGF2 and excreted in urine. It is also increased in patients with asthma, but its production, thus excretion, may be influenced by corticosteroid therapy [33]. Bromotyrosine (BrTyr) is another biomarker that originates from protein oxidation in eosinophils. Urinary levels of BrTyr are significantly higher in patients with asthma and even higher during exacerbation.

It has been suggested in a few studies with a small number of adult patients that during exacerbation the levels of threonine, alanine, carnitine, acetyl carnitine, and trimethylamine N-oxide

were slightly increased, which can be caused not only by the above-described oxidative stress but also by food and drug intake. Some metabolite urine concentrations were lower than usual: acetate, citrate, malonate, and others. Alkane and aldehyde levels were found to be increased in urine; also, the levels of carnitine and acetyl carnitine, which are essential in the process of fatty acid transport into mitochondria, were high in urine of patients with asthma [34]. Other potential biomarkers such as club cell protein 16 (CC16), as a biomarker of epithelial dysfunction, have been studied in urine of patients with asthma. One study in Chinese children showed lower levels of CC16 in asthmatic children [35].

8. Noninvasive biomarkers of asthmatic phenotypes

Over the past decade, the most important advance in the field of asthma has been the recognition of asthma as a syndrome or heterogeneous disease with several clinical presentations or phenotypes. Biomarkers help define the specific pathology of different asthma phenotypes and identify potential therapeutic targets. However, a number of biomarkers have been identified that help define asthma phenotypes most likely than reflect responsiveness to specific therapies. Noninvasive biomarkers such as FENO or sputum cells usually reflect the main inflammatory phenotypes of asthma. Eosinophilic phenotype having more than 3% eosinophils in the sputum is likely to reflect ongoing adaptive immunity in response to allergen. Several biomarkers of eosinophilic asthma, except the percentage of eosinophil, are easily available in clinical practice, such as blood eosinophils, serum-specific IgE, exhaled nitric oxide, or serum periostin level. A significant proportion of asthmatic patients, particularly those with severe disease, do not have a TH2-enhanced phenotype (TH-2 low) [9, 36]. Patients with a non-TH2 phenotype can be further split in two inflammatory phenotypes depending on the level of their airway neutrophilic inflammation: paucigranulocytic and neutrophilic [37]. Neutrophilic asthma as more than 76% neutrophils in the sputum is thought to reflect innate immune system activation in response to pollutants or infectious agents, mixed granulocytic asthma when both inflammatory cells are increased, and paucigranulocytic asthma is thought to be not inflammatory and characterized by smooth muscle dysfunction. Among severe asthmatics, a subgroup characterized by noneosinophilic inflammation was described [38]. We currently lack of user-friendly biomarkers of neutrophilic asthma and airway remodeling. This absence of biomarkers for these patterns of inflammation has made it difficult to recognized subjects who might respond to biologics that target this pathway [38].

9. Noninvasive biomarkers of asthmatic endotypes

Asthma is increasingly recognized as a heterogeneous group of diseases (syndrome) caused by multiple inflammatory pathogenic processes or endotypes. Recently, the definition of the term "endotype," describing a specific pathogenic mechanism leading to the clinical presentation of asthma. Two major asthmatic endotypes have been recognized: TH2-high, manifested by increased eosinophils in the sputum and airways, and TH2-low, with increased neutrophils or a paucigranulocytic cells. Using these classifications and specific biomarkers has led to promising

new therapeutics, often biologics, especially for TH2-high asthma. Many studies of asthmatic endotypes have assessed granulocyte populations in induced sputum. Increased percentage of sputum neutrophil usually represents an increase in IL-17-driven neutrophil recruitment or a relative reduction in other inflammatory cells such as eosinophils [39]. Thus, neutrophil activation state rather than number may be a more important indicator of their contribution to asthma severity, as an indicator of TH2-low endotype. From the other side, nitric oxide is produced by the action of iNOS encoded by the *NOS2* gene, and eosinophils are mobilized by chemokines such as eotaxin-3 encoded by the *CCL26* gene, highly correlated with the TH2 domination. Therefore, available noninvasive biomarkers such as sputum cell analysis or FENO can indirectly represent certain type 2-driven inflammation of asthmatic endotype [40]. The TH2-low endotype does not have any readily available point-of-care biomarkers, so TH2-low asthma is often diagnosed based on a lack of TH2-high biomarkers [41]. The TH2-low endotype characterized greater resistance to steroids and the development of therapies. Advances have been made with regard to sputum cytokine analysis and might also help to guide future treatment of severe asthma. Several other noninvasive biomarkers have been described in different asthma endotypes, but most of them are not commonly available or still need external validation [33].

10. Noninvasive biomarkers and asthma control

Asthma is a heterogeneous inflammatory disorder with several different phenotypes and a nonspecific clinical presentation. Even more, the usually used pulmonary function tests are insensitive and often normal or do not correspond to the disease evolvement [33]. Given the different etiology of asthma subtypes, the therapy is adjusted and needs to be evaluated throughout the duration of treatment. For that purpose a number of biomarkers have been studied for the last 30 years.

One of the longest in use is the measurement of the fraction of nitric oxide in exhaled breath (FENO). Nitric oxide (NO) is generated by three nitric oxide synthase isoenzymes, one of them being inducible (NOS2) that produces most of the exhaled NO. In patients with asthma, especially eosinophilic airway inflammation, the NOS2 overexpression can be reduced by inhaled corticosteroid therapy. This effect is used for predicting the efficacy and monitoring of the ICS therapy in patients with asthma [33]. However, the FENO measurement results can be influenced by flow rate, nasal contamination, ambient air, age, height, gender, race, spirometry or exercise before testing, diet, and smoke exposure [42]. In general, low FENO levels seem to be useful in predicting the asthma phenotypes that will respond poorly to ICS treatment [42]. When the asthma is responsive to ICS, the FENO levels correspond in a dose-dependent manner with ICS [42]. Nevertheless, the method still needs to be further evaluated in studies with standardized protocols.

Exhaled breath has recently been studied in a different setting; namely, after cooling the exhaled breath, a condensate (EBC) containing volatile and nonvolatile particles is produced and can be analyzed for existence of numerous biomarkers. The acidity of EBC is high in asthmatics, but after inducing anti-inflammatory therapy, it rapidly returns to normal values [33]. The total nitrite/nitrate levels have been found to be increased in pediatric asthma

patients compared to healthy controls; still, the results are conflicting regarding the association to asthma severity [42]. Levels of H_2O_2 increase with asthma severity so it plays a role in monitoring disease control and response to steroid treatment as the levels correspond with inducement of steroid therapy [42]. EBC in patients with asthma contains higher concentrations of 8-isoprostane both in children and in adults, when compared to healthy controls [42]. The level of 8-isoprostane is associated with asthma control and severity and, thus, can be used as a monitoring tool.

In combination with nitric oxide, interferon-gamma (IFN-γ), and interleukin-4 (IL-4) measurements in EBC, the level of 8-isoprostane can be used as a good marker for assessing asthma control [42].

However, there are many indices that the EBC contains biomarkers that could be used as a tool to control asthma progression and therapy adjustments; it is still a method primarily used in research setting. The metabolomic and proteomic methods are required in order to have EBC analysis in clinical use, which subsequently generates low-cost effectiveness of the methods at present [43].

Induced sputum is another source of biomarkers that can be used for asthma disease control. As a method it is safe, noninvasive, and thus usable in pediatrics. It contains cell phase (eosinophils and neutrophils) and supernatant with cytokines. Sputum eosinophil count is a key marker of asthma severity and responsiveness to steroid therapy. The number of eosinophils correlates well with asthma severity and is predictive of asthma exacerbation. Elevated levels of eosinophil cationic protein (ECP), IL-4, IL-5, IL-13, TNF-α, IL-6, IL-12, and granulocyte macrophage colony stimulator factor have been found in sputum supernatant of asthma patients [33]. Several studies have challenged the usage of induced sputum analysis for asthma control, but it seems that the results are contradictory so it needs further testing, and for the moment, the method has not been proven accurate enough to be used for asthma monitoring in childhood asthma [43].

Recently, urine has been studied as one of possible sources of biomarkers for asthma disease monitoring. The studies have, so far, found that only leukotriene E4 and bromotyrosine levels are high and associated with disease severity, exacerbations, and aspirin intake [33].

11. Noninvasive biomarkers and asthma therapy

The use of biomarkers in asthma is restrictive because knowledge of the asthma phenotypes is incomplete. The concept of better endotyping asthma can give precision medicine useful data necessary to develop new therapies. Recent trials evaluating biological therapies targeting IgE, IL-5, IL-4/IL-13, and IL-17 have utilized predictive markers to identify patients who might benefit from therapy. Multiple biomarkers including sputum eosinophil count, blood eosinophil count, FENO, and serum periostin have been used to identify patients with a good response to targeted medications (**Table 1**) [44–47]. Till now, relevant biomarkers that can be useful in the management of asthma are mainly related to TH2 response

	Biological sample	Exhaled air	Sputum		Blood						Urine
Target	**Drug**	**FENO**	**eo**	**neu**	**eo**	**IgE[a]**	**Periostin**	**IL-13**	**IL-17**	**DPP-4**	**LT 4E**
T2 biomarkers											
	Glucocorticoid	•	•								
IgE	Omalizumab	•	•		•		•				
IL-5	Mepolizumab	•			•						
IL-5	Reslizumab		•		•						
IL-5	Benralizumab	•			•						
IL4/IL-13	Dupilumab	•			•		•				
IL-13	Lebrikizumab	•					•				
IL-13	Tralokinumab						•	•			
DPA	Fevipiprant		•							•	
LT	LTA										•
Non-T2 biomarkers											
	Azithromycin	•		•[b]	•						
	Clarithromycin			•							
IL-17	Brodalumab			•[c]							
CXCR2	ACD5096			•[c]							

[a]Determines eligibility for omalizumab, but the level is not predictive for response

[b]Trial did not evaluate sputum neutrophil counts

[c]Trial did not demonstrate clinical improvement

Legend: eo, Eosinophils; neu, neutrophils; IL, interleukin; DPP-4, dipeptidyl peptidase-4; LT 4E, leukotriene 4E; CXCR2, CXC chemokine receptor 2 (Adapted according to Medrek et al. [45])

Table 1. Biomarkers predictive of response to different asthma therapies.

[45]. These biomarkers are considered more steroid-responsive [38]. The eosinophil counts has proven to be useful in the clinical arena in helping to predict short-term response to inhaled corticosteroids (ICS) and tailor the dose of ICS in the severe patients [32]. Sputum eosinophil percentage acts as a key marker and correlates with severe exacerbations and AHR. Also, it can be useful in a panel of biomarkers to select patients who may benefit from IL-5 targeted therapies, including reslizumab, mepolizumab, and benralizumab [48]. Blood eosinophils as surrogate markers for sputum eosinophilia are associated with relevant outcomes and are more readily measureable. New evidence supports fraction of exhaled nitric oxide (FENO)-based treatment algorithms for cost-effective maintenance of asthma control/quality of life. Serum and sputum-derived periostin are biomarkers of lung function decline and associated with eosinophilic airway inflammation. Biomarker panels may improve predictive value as shown for the combination of FENO/urinary bromotyrosine in prediction

of steroid responsiveness. Novel biological therapies are proven effective in biomarker-selected populations. Biomarkers including blood eosinophils and FENO are proven to have utility for the effective administration of steroidal and novel biological therapies in asthma, allowing individualized treatment. According to experience of many investigators, the common cause of persistently elevated FENO despite therapy is poor compliance, but this marker is not validated [6]. The complexity and heterogeneity of the asthma request different approaches of phenotyping patients. Used and clustering omics data will provide a better chance of phenotyping asthma based on disease mechanism with composite set of markers obtained for each endotype. Probably, new biomarkers will replace currently available biomarkers and be more specific for both T2 and non-T2 pathways. According to some authors, novel approach is not based on developing new techniques than combining known biomarkers to increase their predictive values. Personalized medicine will allow more precision therapy and also provide novel targets and new treatment for each defined [46]. The future of personalized medicine will depend of availability of accurate and reliable predictive biomarkers.

12. Noninvasive biomarkers of childhood asthma

Asthma represents the most common chronic respiratory disease in children. Whereas preschool children present with multitrigger and viral wheeze, in school children, asthma is usually classified as allergic and non-allergic. For both, the underlying immunological mechanisms are not yet quite understood. Treatment is still prescribed unrelated of underlying mechanisms, and often asthma control in children has not been achieved. Nevertheless, the spectrum of asthma in clinical presentation is broad, and both symptoms and lung function may not always reflect the underlying airway inflammation or endotype [49]. Therefore, in recent years, following the example of adult asthmatics is trying to differentiate specific asthmatic phenotypes as well as endotypes in children. Several studies aiming to identify endotypes are underway, and their relevance for clinical monitoring and subsequent treatment options is still a subject of discussion [50]. For these reasons, the identification of objective biomarkers of childhood asthma phenotype/endotype, which may guide diagnosis, management, and treatment of asthmatic children and might have a role in the development of personalized approach [51]. That is why the availability of noninvasive and validated biomarkers to study and monitor disease is of relevance especially in childhood asthma [52]. Identification of clinically applicable noninvasive biomarkers such as biomarkers in EBC has been of particular interest in personalized diagnosis and treatment of asthma in children [53]. The utility of noninvasive biomarkers in routine clinical practice for monitoring inflammation in children with asthma is undefined, apart from FENO measurements. Sputum eosinophilia, EBC, and urinary leukotrienes are still not applied in routine clinical practice. Despite the development of new biomarkers or new immunological molecules, the complex puzzle of childhood asthma is still far from being completed (**Table 2**) [54].

Biological sample	Biomarker	Therapy response	Diagnostic	Prognostic
Exhaled air	FENO	x	x	
	EBC		x	x
	EBT		x	
	e-Nose		x	
Sputum	eo	x	x	x
	neu		x	
	IL-4		x	x
	IL-5			x
	IL-6			x
	IL-12			x
	IL-13			x
	ECP		x	x
	LT			x
	TNF-α			x
	CSF			x
	GM-CSF			x
	IL-8			x
	Neurokinin			x
	Metalloproteinase			x
	THF-β			x
	Procollagen synthesis peptides			x
Blood	eo	x	x	x
	IgE	x	x	
	Periostin	x	x	
	IL-13	x	x	
	IL-17	x	x	
	DPP-4	x	x	
Urine	LT E4	x	x	x
	EPX	x	x	
	11β-PGF2	x	x	
	BrTyr		x	x
	CC16		x	

Table 2. Biomarkers in asthma.

13. Conclusion

Over the past decades, a great emphasis has been put into developing and researching biomarkers, as well as noninvasive biomarkers in monitoring of inflammation and treatment of asthmatics. The three most promising biomarkers in clinical practice currently are analysis of cells in induced sputum, FENO, and biomarkers in EBC. In the past years, the progress has been made in the discovery, application, and implementation of new, especially noninvasive biomarkers in asthmatic patients. Although now-available noninvasive biomarkers have marked its benefits, their roles are still too limited and nonspecific for identifying at-risk patients, recognitions of specific asthma pattern (phenotype or endotype), and selection of specific and the most helpful treatment, particularly biologics. In the near future, the role of biomarkers in achieving personalized medicine will be critical.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

Abbreviations

ACQ	Asthma control questionnaire
AHR	Airway hyperreactivity
ALF	Airway lining fluid
BrTyr	Bromotyrosine
CC16	Club cell protein 16
CXCR2	CXC chemokine receptor 2
DPP-4	Dipeptidyl peptidase-4
EBC	Exhaled breath condensate
EBT	Exhaled breath temperature
ECP	Eosinophil cationic protein
e-Nose	Electronic nose
eo	Eosinophils
EPX	Eosinophil protein X
ERS	European Respiratory Society

FENO	Fraction of exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GC-MC	Gas chromatography-mass spectrometry
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LT 4E	Leukotriene 4E
neu	Neutrophils
NO	Nitric oxide
PGD2	Prostaglandin D2
VOC	Volatile organic compound

Author details

Mirjana Turkalj[1,2,3]*, Damir Erceg[1,2,3] and Iva Dumbović Dubravčić[4]

*Address all correspondence to: turkalj@bolnica-srebrnjak.hr

1 Srebrnjak Children's Hospital, Zagreb, Croatia

2 Medical School University of Osijek, Osijek, Croatia

3 Catholic University of Croatia, Zagreb, Croatia

4 Institute for Anthropological Research, Zagreb, Croatia

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Chapter 2

Epidemiological Aspects of Rhinitis and Asthma: Comorbidity or United Airway Disease

Sanela Domuz Vujnovic and Adrijana Domuz

Additional information is available at the end of the chapter

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Abstract

Bearing in mind the results of the epidemiological studies, the logical question arises whether allergic rhinitis represents an earlier clinical manifestation of allergic airway disease or itself is causative for asthma. Comorbidity or one disease, the diagnosis of allergic rhinitis often precedes the development of asthma. Literature reports that 40–90% of asthmatics have symptoms of allergic rhinitis. The epidemiological evidence also suggests that allergic rhinitis and asthma radially presented one united airway disease with two-stage than two separate diseases. Symptoms of one disease often predominate and are unrecognized or hidden of another disease even if they exist. The epidemiology evidence of comorbidity of allergic rhinitis and asthma confirmed the new concept of the united airway diseases. Despite the evidence of the correlation between allergic rhinitis and asthma, there is some resistance in clinical practice in recognizing this link.

Keywords: asthma, allergic rhinitis, united airway disease, epidemiology, prevalence, comorbidity, respiratory symptoms

1. Introduction

We have to agree with Togias [1] that the respiratory system has been one of the victims of fragmented medical knowledge. The respiratory system is most often viewed as two separate systems, upper and lower. These have resulted in lost opportunities to fully understand the function of the respiratory system [1]. Upper and lower respiratory systems have similarities in histology, physiology, and pathophysiology [2]. The nose warms, filters, and humidifies inhaled air. Impaired air warming and humidification by the nose may cause bronchoconstriction. A reduced function of the nose can be caused by congestion forces the patient to

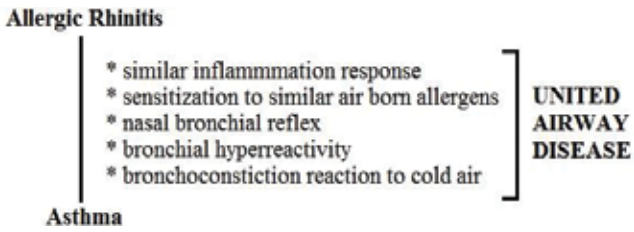

Figure 1. Possible link between asthma and allergic rhinitis.

mouth breathing. Also, there are similarities in inflammation response between allergic rhinitis and asthma [3, 4]. Allergic rhinitis and asthma are frequently associated with sensitization to similar airborne allergens [5]. Some authors suggest the existence of a nasal-bronchial reflex as a cause of bronchial reactivity in a patient with nasal inflammation [6, 7]. That's why recent studies suggest new theory or concept that these two diseases should be viewed as united diseases (**Figure 1**) [8, 9]. The epidemiology evidence of comorbidity of allergic rhinitis and asthma confirmed the new concept of the united airway diseases.

Comorbidity of allergic rhinitis in asthmatics results in frequent emergency visits, asthma exacerbation, asthma-related hospitalizations, and higher asthma-related medical costs [4]. Despite the evidence of the correlation between allergic rhinitis and asthma, there is some resistance in clinical practice in recognizing this link [10]. Also, the guidelines for the treatment of allergic rhinitis and asthma are inconsistently implemented. The consequences of this are a very large number of patients with inadequate diagnosis, no treatment, and poor control of the disease [11, 12].

Most of the epidemiological studies investigate only one allergic disease, asthma or rhinitis. In these studies, another allergic disease was not observed as a comorbidity or a confounding factor. Studies that consider asthma and rhinitis as comorbidity are scarce, but the results of available studies showed that these two diseases are in a high percentage in comorbidity. The percentage of comorbidity showed continuity through different ages of the respondents. A high percentage (70–90%) of rhinitis symptoms in asthmatics was presented in children and the elderly population [13–15].

Despite its high comorbidity, there are surprisingly scarce studies about the treatment of AR in children with asthma or vice versa [14, 15]. Children with allergic rhinitis comorbidity were more likely to have incomplete asthma control in Groot et al. study [15].

2. Epidemiological evidence for the link between allergic rhinitis and asthma

The World Health Organization (WHO) through the Allergic Rhinitis and its Impact on Asthma (ARIA) program tried to understand the possible links between allergic rhinitis and asthma [16]. According to the ARIA study, patients with severe persistent rhinitis more likely

have comorbidity with asthma [16]. Epidemiological evidence also suggests coexistence of asthma and allergic rhinitis in the same patients [17]. Symptoms of one disease often predominate and are unrecognized or hidden of another disease even they exist [2]. The epidemiological evidence also suggests that it is radially one disease with two stages than two separate diseases. Underdiagnosis of allergic rhinitis in asthmatics patients is common. Comorbid allergic rhinitis has a clinically relevant effect on asthma, especially on hospitalization and emergency visits [12]. Treating allergic rhinitis in these patients decreased asthma-related medication utilization [17]. Patients with allergic rhinitis also can be underdiagnosed with asthma [12].

2.1. Prevalence of allergic rhinitis and asthma

The prevalence of allergic rhinitis and asthma has increased worldwide over recent decades [13, 18].

Studies appear to indicate that the changes in the prevalence of allergic rhinitis and asthma differ, but they were not designed to show the variation of the link between these two diseases [16]. Epidemiological studies have no standard set of diagnostic criteria for allergic rhinitis or asthma, so it is very difficult to compare the results. Most of the studies used a questionnaire to define a prevalence, or they are self-reported-based study.

2.1.1. Asthma

A number of epidemiologic studies have reported striking differences in asthma prevalence. The largest multicentric study on asthma prevalence in children the International Study of Asthma and Allergies in Children (ISAAC) showed the asthma prevalence increment trend in children in the period from 1994 to 1999 [19]. The lowest asthma prevalence symptoms values in children aged 6–7 years were in the Indian subcontinent, while the highest asthma prevalence symptoms were in Latin America, North America, and Oceania [19, 20]. For the older age group (13–14 years), the lowest prevalence was in the region of Asia and Pacific, Eastern Mediterranean, and the Indian subcontinent, while children from North America had the highest frequency of asthma symptoms [19, 20]. Wheezing prevalence in the last 12 months also had a similar movement trend, with the lowest prevalence in North and Eastern Europe (5%) and the highest in the region of Latin America and Oceania (>20%) [19]. However, a different trend pattern of severe asthma symptom prevalence movement was noticed. Africa, the Indian subcontinent and Eastern Mediterranean had the highest asthma prevalence characterized with a severe form of asthma in children, while children in Latin America had the lowest prevalence of severe asthma symptoms [19]. Twenty-one centers that participated in the multicentric study had the asthma prevalence in children larger than 20%, while seventeen centers had the prevalence lower than 5% [19, 21].

Generally, the prevalence of asthma in children showed the northwest-southeast gradient movement [22]. This kind of trend is especially expressed in eastern continent. The results of ISAAC study show the highest asthma prevalence in English-speaking countries and Latin America and the higher prevalence in West compared to East Europe and the lowest in Asia

and Africa regions [19]. The Great Britain has the highest asthma prevalence in children (32%), then Bulgaria, Czech Republic, Ireland, and Norway. The prevalence in Albania and Greek was the lowest (<5%) [19, 21].

Prevalence of asthma among the elderly population was 10.9% in the study by Pite et al. [13]. The prevalence of asthma increased with the number of rhinitis symptoms, from 2.1% in no rhinitis symptoms group to 44.4% in nasal symptoms plus ocular symptoms group [13].

2.1.2. Allergic rhinitis

Allergic rhinitis has increased in prevalence during last decades with the highest prevalence among children and adolescents [7, 23–25].

The prevalence of rhinitis among the 6- to 7-year-old children was 6.4% in Eastern and Northern Europe and 7.3% in Western Europe [26]. Higher prevalence of rhinitis symptom was among older children (13–14 years old) where 10.5% children in Eastern and Northern Europe and 14.5% in Western Europe have rhinitis symptoms. Children from Georgia had the lowest prevalence (2.8%), while children from Polish (18.9%) and Isle of Man (20.2%) had the highest prevalence of rhinitis [26]. It was found that countries with a low prevalence of asthma also had a low prevalence of rhinitis [26]. In addition to the European continent, the highest prevalence of rhinitis was observed in younger children in Latin America (12%) and older children on the African continent (21.7%). The lowest prevalence of rhinitis in the 6- to 7-year-old children was in Africa (3.6%) and the Indian Subcontinent (3.9%) while in older children in the Indian Subcontinent (10%) [26].

The recent studies suggest a higher prevalence of rhinitis among the middle-aged population (20–28%) [23, 25, 27]. Pite et al. study showed that rhinitis was a highly prevalent but underdiagnosed and undertreated disease in the elderly population [13]. About 80% of patients had rhinitis symptoms, but only half of them had a diagnosis and/or treatment [13].

2.2. Comorbidity of allergic rhinitis and asthma

Epidemiological studies show significant comorbidity of these two diseases. Literature reports that 40–90% of asthmatics have symptoms of allergic rhinitis, while patients with allergic rhinitis have significantly less prevalence of asthma symptoms (10–40%) (**Figure 2**) [16, 28].

However, it should be emphasized that the prevalence of allergic rhinitis in asthmatics is significantly higher than in the general population (10–20%). Conversely, there is a significantly higher prevalence of asthma symptoms among patients with allergic rhinitis than the general population (an average of 5–15%). The association between allergic rhinitis and asthma had been examined in several studies. The strength of the association with asthma increased with increased persistence and severity of rhinitis [13]. The prevalence of asthma increased with the number of rhinitis symptoms, from 2.1% in no rhinitis symptoms group to 44.4% in nasal symptoms plus ocular symptoms group [13]. A French study showed that 58% of asthmatics children had symptoms of allergic rhinitis [30]; the Italian study showed even higher percentage (70%) [29]. Prevalence of allergic rhinitis in patients with classic asthma was 50–69% in the

study by Tajiri et al. [4]. Among patients with physician-diagnosed asthma, 64% had allergic rhinitis in the study by Eriksson et al. [31]. Symptoms of allergic rhinitis were more common if asthma symptoms were more severe [30, 32]. Children with exercise-induced asthma have a significantly higher prevalence of allergic rhinitis symptoms [32]. The epidemiological evidence consistently demonstrates the coexistence of allergic rhinitis and asthma [17].

The majority of asthmatic patients have seasonal or persistent allergic rhinitis [17, 33]. Also, the presence of allergic rhinitis in asthmatics has been confirmed as a marker of asthma severity [32, 33]. A higher prevalence of allergic rhinitis was observed among children who reported at least four wheezing episodes in the last year or sleep disorders due to acute episodes [32, 34]. Consequently, better asthma control can be achieved if the diagnosis and treatment of allergic rhinitis are adequately done [15]. Comorbidity of allergic rhinitis and other variant forms of asthma (cough variant, exercise-induced) has also been observed in epidemiological studies [4, 32]. Many patients with allergic rhinitis do not have symptoms of classical asthma, but they present with airway hyperresponsiveness and subclinical inflammation of the lower respiratory airway [35]. The results of previous studies showed that almost 50% of patients with bronchial hyperreactivity reported no respiratory symptoms [36]. These patients usually develop asthma but remain underdiagnosed with asthma [12, 28]. Also, allergic rhinitis is not appropriate recognition in patients with asthma [28, 37]. Many patients with allergic rhinitis self-manage the symptoms or do not recognize allergic rhinitis as a condition needing treatment or physicians help [12]. The Portuguese study showed that more than half of patients with rhinitis symptoms had no diagnosis by a physician [13]. This shows that these patients are untreated for allergic rhinitis. It is important to emphasize that patients with mild forms of allergic rhinitis or asthma remain in high percentage without diagnosis and adequate treatment [32]. Esteban et al. found in their study that 53% asthmatics children were underdiagnosed with allergic rhinitis, and asthma was not well controlled in 77% of these children. Only 33% of the children with allergic rhinitis diagnosis were receiving a treatment by ARIA recommendations. Children with poorly controlled allergic rhinitis had poorer asthma control [11].

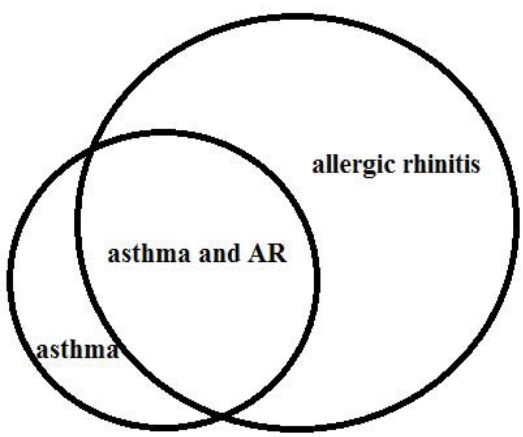

Figure 2. Prevalence and comorbidity of allergic rhinitis and asthma.

Untreated allergic rhinitis in asthmatics contributed to severity symptoms, exacerbation, and uncontrolled asthma [16, 28]. The authors reported that treatment of allergic rhinitis was associated with reduced risk of emergency visits and hospitalization for asthma [3].

3. Allergic rhinitis as risk factor for asthma

Bearing in mind the results of the epidemiological studies, the logical question arises whether allergic rhinitis represents an earlier clinical manifestation of allergic airway disease or itself is causative for asthma [16, 17]. Comorbidity or one disease, the diagnosis of allergic rhinitis often precedes the development of asthma [4, 12]. Studies undoubtedly suggest that allergic rhinitis is a risk factor for asthma [4]. A pathophysiological mechanism which can explain the increased risk of developing asthma in patients with allergic rhinitis is airway hyperresponsiveness. Even 40% of patients with allergic rhinitis showed hyperreactivity to methacholine challenge. Such patients are at greater risk to develop asthma during the next 4–5 years [12]. Also, allergic rhinitis during childhood was associated with increased risk of asthma development in preadolescence and adolescence [28]. The Children's Respiratory Study showed that allergic rhinitis in the first year of life was associated with a risk of developing asthma by 6 years of age [38]. The study by Settipane et al. showed that significantly more (10.5%) of the students diagnosed with allergic rhinitis went on the develop asthma compared with those who did not have allergic rhinitis (3.6%) [39]. The presence of bronchial hyperresponsiveness increased the risk for severe symptoms of allergic rhinitis and asthma and earlier development of asthma in children with allergic rhinitis [12]. It is important to recognize bronchial hyperresponsiveness as a marker of prognostic significance [17]. Epidemiological studies suggest that patients with bronchial hyperresponsiveness without symptoms of classic asthma are more often underdiagnosed with asthma [28].

4. Atopic march

The concept of the atopic march was developed to describe the progression of atopic disorders from atopic dermatitis (AD) in infants to allergic rhinitis and asthma in children [40, 41]. The theory of atopic march implies that young children with atopic dermatitis or food allergy may develop airway allergy such as asthma or allergic rhinitis later in life [40, 42].

The concept of atopic march has been supported by cross-sectional and longitudinal studies [40, 42]. Atopic dermatitis as the first step in the development of atopic march occurs in 45% of children in the first 6 months of life and during the first year of life in 60% of children. In children with atopic dermatitis in the first 2 years of life, an average of 50% of these children develops asthma during subsequent years [42]. The occurrence of only one allergic manifestation, such as recurrent wheeze, eczema, or food allergy, during infancy, was associated with a good prognosis, where over 70% were symptom-free at 8 years of age. Among the children with two or more of any allergic manifestations in infancy, more than half had any allergic disease at 8 years of age [43]. In addition, comorbidity increased from infancy to 8 years of age

as a consequence of the increasing prevalence of asthma and allergic rhinitis. Furthermore, the more allergic manifestations a child had in infancy, the greater the risk of allergic disease and comorbidity at 8 years of age [43]. In late adulthood, allergic symptoms generally become less frequent and tend to disappear, but in some, new-onset allergy or asthma may develop in old age [44]. Results of studies showed that the mean age at onset of atopic comorbidities was 1.8 ± 1.0 years for food allergy, 2.2 ± 1.1 years for asthma, 2.3 ± 1.3 years for allergic conjunctivitis, and 2.4 ± 1.3 years for allergic rhinitis [45]. A systematic review of the literature by van der Hulst et al. showed that there is an increased risk of developing asthma by 6 years among children with eczema [46]. The pooled OR for the risk of asthma after eczema, compared with children without eczema, in birth cohort studies was 2.14. In eczema cohort studies, the prevalence of asthma by the age of 6 years was 29.5%. The proportion of children with eczema developing asthma is clearly higher than among those without eczema, and the "rates" for asthma are three- to fourfold higher than in the general population [46]. However, asthma develops in only approximately one in every three children with eczema. Kapoor et al. examined the prevalence of allergic rhinitis and asthma in 2270 children with physician-confirmed AD and found that by 3 years of age, nearly 66% of the subjects reported to have allergic rhinitis, asthma, or both, and the presence of these diseases correlated with poor AD control [47]. These results should be interpreted with caution because of the heterogeneity of the cohorts.

The Tasmanian Longitudinal Health Study investigated the influence of eczema on the development of asthma from childhood to adult life and found that childhood eczema was significantly associated with new-onset asthma in three separate life stages: preadolescence (hazard ratio 1.70; 95% confidence interval 1.05–2.75), adolescence (2.14; 1.33–3.46), and adult life (1.63; 1.28–2.09) [48]. Results from another two cohorts studies, the Melbourne Atopic Cohort Study (MACS) and the LISAplus study, showed that food sensitization in the first 2 years of life increased the risk of subsequent asthma and allergic rhinitis (MACS OR = 8.3 for asthma and aOR = 3.9 for allergic rhinitis; LISAplus OR = 14.4 for asthma and OR = 7.6 for allergic rhinitis) [49].

The risk of developing atopic diseases is complex, and the temporal pattern described in the atopic march may not be a simple progression [40, 43]. Studies found that many individual children do not follow the classical allergic march [49, 50]. For this reason, different patterns of allergic morbidity and the coexistence of the different manifestations, rather than progressive development of one underlying disease, have been suggested [43]. Several studies have suggested that, even though they are associated, the different combinations of allergic manifestations seen over time suggest the coexistence rather than the progressive development of the same underlying disease [43]. Children with early eczema who develop asthma and allergic rhinitis might represent one specific phenotype of eczema, characterized by eczema plus either wheezing or a specific pattern of sensitization [43]. The results of MAS Study showed that children with eczema and without early wheeze were not at increased risk for the development of asthma. These results implied that eczema alone may not be the first most predictive phenotype in the atopic march [51]. Eczema before 2 years of age without the cofactor of wheeze before the age of 3 years and without a specific pattern of atopic sensitization was not associated with an increased risk of wheezing at 7 years of age (adjusted OR 1.11). In addition, the authors suggest that the combination of eczema with early wheeze is a distinct phenotype

rather than a representation of a progressive pattern of atopic diseases [51]. However, the risk for development of asthma at 7 years of age among children with early eczema and atopic sensitization to less common antigens but without concomitant wheeze was stronger (adjusted OR, 6.68) than the association between early eczema with early wheezing (adjusted OR, 2.84). This is in consistent with the pattern of the atopic march in which eczema with atopic sensitization presents a higher risk for the development of atopic respiratory disease [52]. The cohort of children with an early-onset AD with a lower rate of sensitization to allergens was associated with a low risk for developing asthma. The cohort of children with multiple sensitizations and with familiar history of asthma had a higher prevalence of asthma than the general population in the study of Amat et al. [53]. Also, studies showed that patients with eczema with specific IgE antibodies to common environmental allergens present by 2 to 4 years of age are at higher risk for progressing in the atopic march to allergic rhinitis and asthma than those with eczema without IgE sensitization [53, 54]. Current evidence suggests that further refining early childhood eczema phenotypes may represent a more robust measure of the first phenotype of the atopic march, with a greater predictive value of identifying those at risk of developing allergic rhinitis and asthma [52].

Likewise, many studies in animal models demonstrate that epidermal barrier dysfunction can be caused by repeated sensitization to allergens to the skin, which leads to phenotypes of AD systemic sensitization and increased risk of allergic rhinitis lung inflammation and airway hyperresponsiveness [43]. A study in a mouse model showed that epicutaneous aeroallergen exposure induces systemic Th2 immunity that predisposes to allergic nasal responses, suggesting that the skin is a potent site for antigen sensitization in the development of experimental allergic rhinitis [43]. Experimental studies showed that epicutaneous sensitization with ovalbumin induced AD and airway hyperresponsiveness to methacholine after challenge with aerosolized ovalbumin [43].

The pathophysiological mechanism of atopic march has been unknown. Skin barrier dysfunctions can explain partly the mechanism of atopic march [50]. Namely, skin barrier defect can promote entry for allergens [50]. Epicutaneous sensitization to aeroallergens has been thought to be responsible, with subsequent migration of sensitized T cell into the nose and airways, for development of allergic upper and lower airway diseases [55]. Sensitization that followed eczema is likely to be a step in the pathophysiological pathway between eczema and asthma [56]. Previous data support the hypothesis that respiratory allergies are secondary to allergic sensitization that occurs after epidermal skin barrier defect [50].

4.1. Conclusion

The atopic march is a useful paradigm to describe the clinically observed progression of atopic diseases in certain children [52]. Whether each step in the march is necessary for progression to the next or further defining of these phenotypes would be more useful in identifying children at risk for developing chronic allergic diseases is still a matter of debate. Allergic manifestations can develop at any point in life. Many children will experience only one or perhaps two atopic manifestations, and the development of these can be interspaced by several years [57]. The progression of allergic disease is not uniform in all atopic children. However, the

coexistence of allergic manifestations in the same child has been shown to be more common than expected by chance alone [43]. Also, it is still unclear why some infants with AD outgrow the disease with increasing age, whereas others will march to develop other allergic diseases [41]. Therefore, it is not uncommon that an adult with "new-onset" asthma are unable to remember whether they had allergic diseases in childhood [57]. A better understanding of what places a subset of children with eczema or allergic rhinitis into the risk group for developing asthma is critically important. "Given that most infants with eczema or early wheezing do not develop rhinitis and asthma, further refinement of these early phenotypes or additional risk factors is important for them to be useful" [52]. It is important to define more precise phenotypes of the early stages of the atopic march that may improve its utility in predicting the development of later atopic diseases [52].

Although it has become evident that the mechanisms by which allergen exposure occurs through impaired skin barriers can initiate systemic allergy and predispose individuals to AD, allergic rhinitis, and asthma, the mechanisms of the atopic march are still largely unknown [41]. The findings of studies support the atopic march theory on a population level. But the concept of atopic march is not the strongest factor at the individual level of children with allergic disease [43].

Author details

Sanela Domuz Vujnovic[1]* and Adrijana Domuz[2]

*Address all correspondence to: drdomuz@gmail.com

1 School of Applied Medical Sciences, Prijedor, Republic of Srpska, Bosnia and Herzegovina

2 Primary Health Center, Republic of Srpska, Bosnia and Herzegovina

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Chapter 3

Meaning of Endotype-Phenotype in Pediatric Respiratory Pathology

Francisco Muñoz-López

Additional information is available at the end of the chapter

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Abstract

Respiratory processes that take place in childhood (preschool and adolescence) have a predominant frequency, especially rhinitis and asthma. Family predisposition and the environment define the characteristics of the endotype and the phenotype. Heritage, both of the genes related to bronchial hyperresponsiveness and those related to atopy (production of specific IgE against allergens and hypereosinophilia) are the fundamental basis of those processes that begin at preschool age and continue into adulthood if they do not receive early and etiological treatment. The physiological vagal hyperresponsiveness of the infant; the environment in which it develops, even from the prenatal phase (pregnant smoker); and viral infections are responsible for frequent bronchial processes in the early years that, sometimes, also extend into adolescence. In summary, the coordination of the endotype and the phenotype has led to the acknowledgement and acceptance of these three tracheobronchial processes: transient early wheezing, non-atopic wheezing, and atopic wheezing/asthma.

Keywords: children, phenotype, endotype, bronchospasm, wheezing, asthma

1. Introduction

The phenotype is defined as "observable characteristic with no direct relationship to a disease process, including physiology, triggers and inflammatory parameters" and the endotype as "distinct disease entities which may be present in cluster of phenotypes, but each defined by a specific biological mechanisms." [1, 2].

The variability of bronchopulmonary processes that take place in childhood makes it difficult to establish the criteria for the definition of asthma and, therefore, the phenotype. Age is one

of the most important determinants of the phenotype in early childhood and adolescence, including determinants from genetics to the environment. In early childhood, airway development, the environment (especially pregnant smoker), and frequent viral infections, without a doubt, have a decisive influence to establish the phenotype. Symptomatology and lung function (especially the specific airway resistance, atopy, and airway hyperresponsiveness (AHR) at age of 3–5 years) identify several groups of variants: only wheeze, wheeze with irritants, chest congestion and cough, wheeze with allergens that correlate to atopy, and AHR. Asthma that began at those ages, usually preceded by rhinitis, usually lasts until adolescence, if an adequate treatment was not carried out, especially based on the etiology (immunotherapy). In some cases, at that age, the causality may be different, environment and acquired habits (especially smoking) that lead to inflammation of the airways, similar to what occurs in adults (occupational asthma). Three variants have been proposed based on the endotypes: mild to intermittent asthma, asthma with severe exacerbations and multiple allergens, and severe obstructive asthma with neutrophilia [2, 3].

Allergic diseases can be predicted taking into account the key factor in their onset, genetic predisposition, since it is inherited as autosomal dominant trait. Knowledge that at least one of the parents suffers from an allergic disease is a factor to consider. In fact, it is the most reliable indicator for predicting predisposition, although not sufficient to predict it accurately. If both parents are allergic, and even more if they are asthmatic, the risk of allergic respiratory disease can be predicted even better. Although the existence of first-degree relatives suffering from allergic disease is considered the most valuable data, among many others that have been studied, the degree of reliability can be specified as 50% of cases.

2. Genetic predisposition: chromosomes and genes involved

The allergic predisposition (atopic) is of a polygenic nature, that is to say, the genes that support the polymorphisms that give rise to the body's abnormal response to substances (allergens) that are well tolerated by most people and which originate the production of specific IgE antibodies (reagins) against proteins with antigenic capacity contained therein. Even with no atopic predisposition, at any age, excessive exposure to allergens equally can cause specific IgE production, with consequent clinical translation.

The genetic basis of asthma is not unique, but depends on a complex polymorphism, and it is not strange that the involvement of the various genes that are supposed to be implicated is not yet known. The allergic reaction is linked to the predominance of Th2 lymphocyte activity and the subsequent increase in specific IgE. Chromosome 11 (11q13) was the first to identify genes involved in its production; in it lies the synthesis of the β chain of the high-affinity IgE receptor.

It is estimated that at least 100 genes are involved in the pathogenesis of atopy and asthma. Some 30 loci on various chromosomes have been linked on the one hand with the function of the airways and another on the production of IgE [4, 5]. Chromosome 5 (5q31-q33) contains the genes that modulate the production of interleukins secreted by Th2 lymphocytes, such as IL-4 and IL-13, responsible for the atopic response when involved in the secretion of IgE by

B lymphocytes (plasma cells), as well as other interleukins (IL-3, IL-5, IL-9) which also intervene. In addition, in the same gene, the protocadherin-1 (PCDH1) that could alter the integrity of the bronchial epithelium, the first line of defense against inhalation of environmental substances, has been identified [6]. On the other hand, the onset of asthma in the pediatric age has linked to chromosome 17q21, the main genetic determinant of the ORMDL3 gene that encodes endoplasmic reticulum proteins, and has also been associated with poor outcome in children exposed to environmental irritants, especially tobacco smoke [7, 8].

Logically, genes related to the allergic reaction are common to other allergic processes, such as those caused by food or drugs mainly, which may be the cause of dermatological (eczema, urticaria), digestive, or anaphylactic processes. Sometimes, because of the same, there is allergic rhinitis, but it must be taken into account that it is not always an exclusive manifestation of the allergy but at the same time, the genes involved in the pulmonary function (airway hyperresponsiveness) can intervene. In these cases, rhinitis precedes asthma, as in many cases eczema manifests itself early in infants who later suffer from asthma.

Based on these data, the respiratory processes of allergy cause are rhinitis, tracheobronchitis, and asthma.

3. Respiratory processes

3.1. Rhinitis

The respiratory mucosa shows structural and functional homogeneity in all areas where it is found with the exception of greater vascularization in the nasal area. Its specific function lies in providing a defense against the noxious agents that so abundantly penetrate through the airways. The entire inner layer of the airway participates in the ciliary defense system with which the epithelial cells are endowed, in addition to the various mucosal glands and cells of the immune system, present in the subepithelial layer throughout the mucous membrane. Likewise, it can present a unified response, although in different ways, against allergens in individuals with an atopic disposition. For this reason, allergic disease is commonly manifested by symptoms that affect the entire mucosa (rhinitis, asthma, rhinosinusitis, rhinoconjunctivitis), although frequently only a partial stretch is affected, with symptoms exclusive to the upper airway.

In most asthma cases, children display rhinitis or rhinopharyngitis during some time prior to symptoms at lower levels of the respiratory tract. Even at birth or in the first months of life, children can display symptoms of allergic rhinitis, although at that age specific sensitization can hardly be demonstrated. The symptoms that can precede the onset of asthma are hydrorrhea, nasal congestion, and sneezing. Later, when asthma is treated correctly and symptoms disappear, rhinitis symptoms—albeit mild—tend to remain as an aftermath.

3.2. Tracheobronchitis

If the concept of asthma is based on the occurrence of dyspnea (shortness of breath is preponderant), episodes of coughing and breathing noises can also lead to an asthma diagnosis.

In many cases (at any age) coughing is productive, and low wheezing is detected by auscultation, sometimes due to tracheobronchial obstruction by mucus secretion or by some degree of constriction of the smooth bronchial muscle. Asthmatic children sometimes display these same symptoms, alternating with dyspnea episodes (**Table 1**).

3.3. Asthma

Even under proper treatment conditions, asthma is usually persistent. Patients experience unexpected relapses, although most children experience clear and progressive improvement, both in terms of seizure frequency and intensity. The speed of improvement largely depends on the prognostic outlook. Many children stop having attacks shortly after starting hyposensitization treatment, and in these cases, a positive prognosis is highly likely. However, another non-negligible group in the framework of undeniable improvement displays a greater tendency to relapse, sometimes as a result of seemingly banal respiratory processes caused by epidemic viral infections or nonspecific triggers, such as change in the weather, overexertion, or exposure to environmental contaminants. In general terms, without a solid underlying statistical basis, it has been estimated that in 75% of cases, childhood asthma is benign and subject to good prognosis, 20% of asthmatic children suffer from a mild form, and the remaining 5% suffer from severe asthma. Children in this 25% group are therefore most likely to suffer from asthma in adulthood [4, 5]. In any case, we must bear in mind that wheezing is a common symptom in other processes which should be considered (**Table 2**).

Cough	Whistling rales	Dyspnea	Expectoration
Rhinopharyngitis	Tracheobronchitis	Wheezing bronchitis	Chronic bronchitis
Sinusitis	Foreign body	Bronchiolitis	Bronchiectasis
Adenoiditis	Mucoviscidosis	Gastro-oesophageal reflux	Pneumonia
Whooping cough	Bronchiectasis	Extrinsic allergic alveolitis	Mucoviscidosis
Tracheobronchitis	Hemosiderosis	Extra-tracheobronchial:	Hemosiderosis
Laryngitis	Lymphadenopathy	• Pleuritis	COPD
Bronchitis	Pulmonary cysts	• Pneumonia	
Bronchiectasis	Immotile cilia syndrome	• Tuberculosis	
Foreign body	Lobular emphysema	• Pulmonary edema	
Gastrooesophageal reflux	Tracheoesophageal fistula	• Etc.	
Inhalation of irritating gases	Eosinophilic bronchitis		
Eosinophilic bronchitis			
COPD			
Psychogenic			

Table 1. Common tracheobronchial symptoms and more frequent processes (other than asthma).

Common	Asthma
	Gastroesophageal reflux
	Infections: bronchiolitis, bronchitis,
	pneumonia, upper respiratory
Uncommon	Bronchopulmonary dysplasia
	Foreign body aspiration
Rare	Bronchiolitis obliterans
	Congenital vascular abnormalities
	Cystic fibrosis
	Immunodeficiency diseases
	Mediastinal masses
	Primary ciliary dyskinesia
	Tracheobronchial anomalies
	Vocal cord dysfunction

Table 2. Causes of wheezing in children.

Several follow-up studies over several years reach different conclusions in the numbers of asthma persisting in adulthood. These differences can be explained by the different criteria taken into account for estimating the persistence of the disease, in addition to the different conditions of patients' lives, such as the workplace, smoking, climate, urban or rural living, etc. It is known that broncholability (airway hyperresponsiveness) persists indefinitely, although with proper and early treatment it can decrease significantly. This weakness can be displayed in unfavorable situations, such as a viral infection and excessive exposure to environmental pollutants, with the onset of sporadic respiratory symptoms (wheezing) which should not be labeled as asthma and much less be interpreted as asthma relapse.

It is difficult to establish a prognosis beforehand, although some data are available to evaluate it. The immune system matures throughout childhood, so most infections occur in the early years of life. Depending on their environment, children may experience up to a hundred infections in their first 8 or 10 years of life, i.e., an average of one infection per month, so that the immune system receives sufficient stimuli for maturation. While they do not always appear with a very striking clinical picture, these respiratory tract infections can trigger bronchial obstructions of varying intensity. This can result in the false diagnosis of asthma, without the existence of a hypersensitivity reaction or inflammation that leaves permanent side effects. As the defense system matures when a child is between 6 and 8, the child stops experiencing bronchial obstruction, and these "false asthma patients" will be the ones who heal spontaneously.

Some endocrine system maturational factors (still undetermined) in some children boost an improvement around puberty, more evident in boys than in girls. But this improvement is only apparent. In most cases it is not uncommon for more or less mild symptoms to appear sporadically, sometimes during physical exercise, in addition to other minor symptoms such as rhinitis or eczema, when present. The typical physical and psychological changes during

this age make asthma patients often underestimate their symptoms and abandon treatment. However, spirometry tests often reveal impaired respiratory function, to varying degrees, predominantly affecting peripheral bronchi ("small airways"), evidenced by the reduced mid-expiratory flow.

To make a prognosis, the location of bronchial obstruction must be determined, and it is not detectable when the respiratory function is checked only by measuring the peak expiratory flow (PEF). The obstruction of peripheral bronchi is an indicator of poor outcome. It has even become established that this data may have prognostic value, so that 7-year-old children without asthma are more likely to develop asthma in the following 6 years if their average expiratory flow is lower than normal. Expanding on this concept, the reduction of mean flow at that age also predicts the persistence of asthma in adults, 25 years later.

3.3.1. Pathogenesis

Asthma is a disease whose onset in childhood has, in most cases, a genetic factor of not only allergic predisposition (production of specific IgE against allergens and eosinophilia) but also factors responsible for airway hyperresponsiveness (AHR). In other cases, especially of later onset, bronchial inflammation, with initial involvement of the respiratory mucosa, asthma is a consequence of environmental irritants or viral infection, in which case neutrophilic is the dominant.

In the pathogenesis of asthma, bronchospasm occurs first aided by the AHR, and it is what characterizes the initial phase of asthma attack. Airway smooth muscle contraction involves the formation of actin-myosin cross bridges with the rate of formation dependent upon the activity of myosin light chain kinase and myosin light chain phosphatase. Subsequently, the release of various proteolytic enzymes of eosinophils (ECP, MBP, EPO, EPX) and phospholipid metabolites (LT, PG, TX) triggers the inflammatory reaction, which is responsible of the prolongation of the crisis as well as the chronicity of the process. Congenital AHR is the consequence of several mutations in the genes encoding β_2-adrenergic receptors of the bronchial smooth muscle, related to the greater sensitivity of the same in the people affects due to the mutation. The consequence of this mutation is the α-adrenergic (constrictor)/β-adrenergic (relaxant) imbalance. In addition, mast cells have been demonstrated in the bronchial smooth muscle of these patients, which undoubtedly have a predominant role in the hyperresponsiveness when the mediators responsible for bronchial smooth muscle constriction and the attraction of eosinophils and neutrophils (histamine, tryptase, chymase) and later those involved in the inflammatory reaction (leukotrienes, prostaglandins, thromboxanes) are relapsed [1, 2].

Genetic predisposition (endotype) can be based either in the mutation that leads to congenital AHR or the multiple factors affecting atopic. The coincidence to both genetic backgrounds determines the early onset of rhinitis/asthma which has led to the conception of different phenotypes. Family atopy is a key factor for the onset of allergic disease in infancy, but the absence of AHR, sometimes, is manifested by skin, digestive, or anaphylactic (food, drug) reactions. If the family atopic predisposition is absent, the AHR that can be secondary to environmental factors will also be basic in the pathogenesis of asthma that in these cases, the onset will be later.

The AHR is responsible for acute and sporadic bronchospasm (episodes of dyspnea). The other symptoms, not sporadic, but habitual of greater or less intensity depending of the gravity, environment, and treatment, are mainly due to the inflammation that accompanies the process, whose cause differs in different circumstances [5–10].

Dominant symptoms, age of onset, persistence, and causes (viruses, allergens, environmental irritants) are the factors that influence the variability of phenotypes, not always persistent from childhood to adulthood, which undoubtedly differentiate the process at the different stages of life.

3.3.2. Prognostic criteria

The beforehand assessment of disease progression can be established based on the following data: family history, child-dependent factors, environment, disease characteristics, and early and correct treatment. The sum of unfavorable data worsens prognosis.

Family genetics, especially parental, increases the risk proportionally to the acuteness of the allergic process (asthma, eczema). Moreover, immunodeficiencies must be taken into account. They favor respiratory infections, especially selective IgA deficiency, which is present very often due to hypersensitivity reactions, perhaps due to an immune compensation mechanism. Within the environment, both the location of the home and the atmosphere within the home may have a significant influence. In terms of age of onset, it should be noted that in the first 2 or 3 years of life, episodes of shortness of breath may occur due to various anatomical-physiological causes (immune immaturity, bronchial constriction, vagal tone) which result in narrowing of the bronchial lumen in various circumstances. This should not be labeled as asthma. Thus, it is estimated that between 45 and 85% of these children in a few years will no longer exhibit symptoms. They are considered "false asthma patients" who will heal spontaneously. The possibility exists for the child to suffer from rhinovirus-induced bronchiolitis leading to significant desquamation of bronchial epithelium and inflammatory reaction which facilitates the passage of pneumo-allergens leading to sensitization, even in the absence of prior atopic predisposition.

Sensitization to multiple allergens is another cause of poor outcome, especially if these involve a fungus. These microorganisms result in a type of asthma which is more difficult to control. With regard to an atopic predisposition, suffering from several allergic diseases is another cause of poor outcome. Atopic eczema is the most influential, in direct proportion to how extensive and stubborn it is.

3.3.3. Evolutionary criteria

Not all children with wheeze at early age will have asthma later; the sex also influences the natural evolution of the process with a shift in severity and prevalence biased toward women after puberty (**Table 3**).

In summary, the evolution of the process can be summarized as follows:

Good evolution: decrease in the number of asthma attacks in 1 year to half or less than the previous year, respiratory function within normal limits.

	Age (year)		
	<5	**5–11**	**12–18**
Prevalence by sex	M > F	M > F	Before puberty: M > F After puberty: F > M
Predominant effector cell	Neutrophil Eosinophil	Eosinophil	Eosinophil
Reticular basement membrane	Begins after the first birthday	Not as thick as adults	Thickening approaches that are seen in adults
Lung function	Measures difficult to obtain	Changes associated with duration of asthma symptoms	Deficits present in those patients who began wheezing before age 3 but might not present in those who began wheezing in later childhood
Incidence of exacerbations	++++	+++	++

Taken from Szefler et al. [11].

Table 3. Pathophysiologic changes of asthma by age.

Moderate evolution: decrease in the number of attacks in 2 years to at least half of the previous year at the start of treatment, improving the intensity of attacks and maintaining an acceptable respiratory function.

Poor evolution: the number and intensity of attacks do not change, and the respiratory function does not improve but actually tends to worsen, with FEF_1 between 70 and 80% of predicted and $FMF_{25–75}$ between 40 and 60% of forecast.

Deterioration: aggravation of the crisis in frequency and/or intensity, with impaired respiratory function: $FEV_1 < 80\%$ and $FMF_{25–75} < 60\%$ of forecast.

3.3.4. Healing criteria

Atopic genetic predisposition is not modified by any therapeutic measure, but clinical signs can be suppressed in a large number of patients with appropriate preventive measures and early treatment, targeting primarily causal aspects (immunotherapy can partly correct the altered immune response).

The clinical criterion is possibly the most valuable with regard to how long the child must be free of symptoms, particularly dyspnea, since sometimes children unexpectedly relapse after a long time of being symptom-free. A widely accepted period of time is 2 years without an attack.

In parallel to the absence of subjective clinical symptoms, the objective assessment of the respiratory function (spirometry tests) is another data factor that must unavoidably be taken into account. This is because children cannot be considered asthma-free if bronchial obstruction persists, although they may be free from obvious symptoms. Certainly, a child with alterations in spirometric values cannot be considered risk-free.

Chronological	2 years without crisis
Functional	Absence of signs of bronchial obstruction (large and small airways)
Airway hyperresponsiveness	Decreased response to allergen inhalation
	Decreased response to methacholine or histamine inhalation
	Decreased response to physical exercise
Immunoallergics	Decreased response to prick test
	Decrease of total IgE
	Increase of IgG (IgG_1–IgG_4)
	Increase of Th1 lymphocytes
	Decrease of basophil degranulation (decrease of histamine release)

Table 4. Asthma healing criteria.

Table 4 shows the different data to be assessed after the etiological treatment (immunotherapy), the results of which will depend on the asthma cure criteria. This brings changes in the immune response (reduction of IgE, increase in IgG_1-IgG_4, and increase in Th1 lymphocytes), together with the decrease in histamine. Bronchial hyperresponsiveness, however, is maintained, although reduced by elimination or reduction of bronchial inflammation, which in itself does not represent a risk of relapse, as it is verified after an average of 10 years after the medical discharge [12].

4. Preschool children

Some anatomo-physiological characteristics of the airways of infants and young children predispose to the occurrence of processes that lead to narrowing or bronchial obstruction, which are manifested by common symptoms, such as cough, dyspnea, and noise or wheezing.

The smaller bronchial caliber is a basic fact that facilitates the obstruction, as a consequence of the inflammation of the mucosa, of the constriction of the smooth muscle or of the increase of the secretion of the tracheobronchial mucous glands. Also known is the physiological vagal tone of the infant, which lasts during the first years of life. Pathologically, bronchial hyperresponsiveness is a fundamental fact in the pathogenesis of asthma. This AHB, by stimulation of the bronchial smooth muscle, is usually secondary to the inflammatory reaction that takes place in various circumstances in the bronchial mucosa, but it is also a characteristic of individuals with atopic predisposition, since there are certain abnormalities in the protein chain of the β-receptors of the smooth muscle.

In relation to the infectious bronchopulmonary disease, so frequent in the first years of life, there is the well-known immaturity of the immune system, which in some children last for several years (transient immunodeficiency of the infant), facilitating the appearance of bronchial inflammatory processes, which they manifest with symptoms partly common to other

tracheobronchial processes. The inflammation of the small airways is correlated with the existence of exhaled nitric oxide (FeNO) whose values have been proposed for the diagnostic confirmation of asthma, even up to school age because it is considered as a potential biomarker to distinguish endotypes. However, despite its strong correlation with atopy, it seems that it can only be considered as a biomarker for transient wheezing but not for persistent wheezing phenotypes.

Viral infections (respiratory syncytial virus (RSV) and rhinovirus (RV)) are a frequent cause of respiratory processes in young children, often transient (bronchiolitis), although in some cases the persistence of chronic inflammation, disrupted epithelium, and airway remodeling can condition the major bronchoconstrictor response to environmental irritants and, especially, to allergens, causing asthma [13].

With this background, it is not uncommon for processes of different causality to manifest clinically with similar symptoms, which can lead to erroneous diagnoses, if the knowledge of differential signs is not in-depth, such as genetic background, habits, and family environment, among others (**Table 5**).

Dominant symptom: cough	Maxillary sinusitis
	Adenoid vegetations
	Rhinopharyngitis
	Whooping cough
	Primary ciliary dyskinesia
Pseudoasmatic symptoms	Infectious pathology
	• Immunodeficiencies
	• Bronchiolitis
	• Bronchitis obliterans
	Tracheobronchial foreign body
	Cystic fibrosis of the pancreas
	Gastroesophageal reflux
	Mediastinal tumors and adenopathies
Less frequent processes	Congenital anomalies
	• Laringo and tracheomalacia
	• Vascular rings
	Alpha-1 antitrypsin deficiency
	Hypersensitivity pneumonitis
	Pulmonary hemosiderosis
	Alveolar proteinosis
	Eosinophilic lung

Table 5. Most outstanding processes for differential diagnosis.

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In a large study (8310 mothers) in which the presence of respiratory symptoms that took place between 6 and 81 months after birth was investigated, the authors reached this conclusion:

1. Sixty-eight percent of the children never had episodes of wheezing .
2. Ten percent had them sporadically, with a prevalence between 18 and 42 months.
3. Eight percent presented them for a long time, between 30 and 69 months.
4. In 2% the prevalence was low until 19 months, increasing after 18 months.
5. Late onset in 5% of the children, in which the prevalence of sibilance lasted up to 42 months in 50% of them.
6. Persistent wheezy (7%) with 65% prevalence at 6 months and approximately 90% prevalence thereafter [14].

In a more recent study, the same authors analyze the need to assess the exhaled nitric oxide fraction (FeNO) together with the respiratory function, family history, and environment in which the child lives, in addition to the treatment received, facts that may condition the persistence of the process for a longer time [15].

A study carried with the purpose of knowing if the different respiratory processes in young children could be related to breastfeeding and its duration finds above all a possible protection against viral infections, but it has not been possible to establish its participation in the establishment of phenotypes related to other respiratory processes.

It is really difficult to establish a certain diagnosis of asthma in the first years of life, since in many cases it is the evolution of symptoms over the years that allows confirming the diagnosis with support of the appropriate immuno-allergological study. The diagnosis of asthma will be reached by previously excluding other possible causes of dyspnea or wheezing. As a more frequent diagnostic alternative, "wheezing bronchitis" would be characterized by single or repeated episodes of dyspnea or wheezing and/or noisy breathing, of variable intensity, which may be febrile, which begin in the first year of life and do not continue more than the third year. In summary, in preschool children this respiratory episodes can be classified as (a) occasional, one episode every 4–6 weeks or less; (b) frequents, more of one episode in 4–6 weeks, isolated intercrisis symptoms, mild; (c) moderate persistence, very frequent exacerbations, symptoms that interfere with daily activities and sleep; and (d) severe persistent, daily or almost daily symptoms, with frequent episodes of dyspnea.

Coinciding with these concepts, different phenotypes of bronchospasm pathology in children have been differentiated, distinguishing asthma and transient bronchitis (wheezy bronchitis) that encompassed various processes suffered by a group of children that after preschool age do not have bronchospasm, a consequence of the predisposing factors. However, it is not always easy to determine the phenotype of a certain patient, and it may even be that over time, as it evolves, there is a need to change the criteria. Hence the need to pay attention to the characteristics of the symptoms and their evolution, in addition to a whole series of

circumstances, such as the suffering other allergic processes by the same child (eczema, milk protein allergy), early onset of the clinic, or the existence of similar pathology among siblings, parents, or other close relatives, environmental contaminants, climate, etc. The lack of family history in approximately 20% of cases adds another obstacle to the diagnosis.

In most children, asthma begins in the first 5 years of life. Different studies indicate that between 15 and 35% of preschool children have had some episode of respiratory difficulty, accompanied or not by wheezing or other respiratory sounds (wheezing bronchitis); however, 60–65% of those children will not suffer a crisis after the third year.

Apart from asthma and wheezing bronchitis, many other bronchopulmonary diseases have an early start, with a symptomatology that may recall those processes, as more frequent, sinusitis, adenoiditis, mucoviscidosis, ciliary dyskinesia, various malformations, gastroesophageal reflux, etc., to be taken into account in all cases.

Physiological factors (reduced bronchial caliber, physiological vagal tone, immune immaturity) tend toward normalization, while pathological factors (familial atopy, congenital or acquired bronchial hyperresponsiveness) depend on their incidence and decrease or increase depending on the circumstance.

5. School age and teenagers

The asthmatic adolescent presents particular characteristics, in part conditioned by the teenager's personality but also, possibly, because this illness has a different expression than in other ages. It is a fact that an undetermined percentage of children improve when reaching adolescence, even being free from symptoms in some asthma cases qualified as mild or moderate. Nevertheless no cases of severe asthma disappear totally at this age. Some undetermined factors, possibly hormone-related, might influence this improvement in males. It should be clarified if this improvement is real and *definitive. Many* children at this age, with sporadic and mild symptoms more or less frequent (coughing, mild dyspnea after exercise), get used to their illness and say they feel well, although it is not rare listen to whistling of different intensity. Even in asymptomatic cases, with normal auscultation, the spirometry presents disturbances that show bronchial obstruction.

The persistence of respiratory processes that begin at preschool age can occur if the phenotype corresponds to the existence of atopic predisposition or, also, in some children infected by rhinovirus (RV) [16]. At these ages, asthma derives predominantly from atopy in relation to Th2 lymphocytes (IgE), eosinophilia, and airway inflammation. Early initiation of adequate treatment avoids the persistence and/or severity of asthma at these ages, especially in cases in which asthma was considered mild or moderate. However, no case of severe asthma stops manifesting at this stage of life and may become chronic due to the persistence of obstruction of the airways, manifesting recurrently serious or episodic, when predisposing factors are scarce. The persistence of asthma in these ages may be due to the intensity of the atopy (association of atopic eczema) and the AHR; the process self-control, failure to comply or the abandon treatment and inadequate medication in the crisis; and family or work environment, smoking, powder, animals, etc.

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Some undetermined factors, possibly hormonal, must influence the improvement and also the inversion that occurs at this age, in terms of frequency by sex, with predominance in the female, predominant in adulthood. In some cases in which the symptomatology is very sporadic, however, spirometry can show alterations that reveal bronchial obstruction that will condition the subsequent evolution. However, in milder cases, it is possible that spirometry remains within normal limits, so the methacholine or histamine test can help demonstrate the hyperresponsiveness.

Four phenotypes related to responsible allergens (especially fungi) and AHR have been distinguished: [1] later sensitization to indoor allergens, [2] multiple early sensitization, [3] early sensitization to outdoor allergens (especially *Alternaria*) and later sensitization to indoor (including *Aspergillus*), and [4] early sensitization to indoor allergens and later sensitization to outdoor allergens [17, 18]. In some cases, asthma begins in adolescence, possibly due to the low familial predisposition of atopy (only uncles or grandparents) and only slight bronchial hyperresponsiveness, which is why it is possible that the environment or the beginning of smoking is responsible for its start [19].

At these ages, coming from the smallest ones or beginning in them, the following phenotypes and endotypes of asthma can be distinguished that usually extend until the adult age:

1. Eosinophilic: allergic, by aspirin, severe hypereosinophilic of late onset, and allergic bronchopulmonary mycosis
2. Prone to exacerbations: allergic, by aspirin, severe hypereosinophilic of late onset, wheezing from a younger age, exacerbation by virus, and premenstrual syndrome
3. Related to obesity: obstruction of air flow, severe steroid dependence, severe hypereosinophilic of late onset
4. Overexertion: athletes, wheezing from preschool age.
5. Fixed airflow limitation: noneosinophilic (neutrophilic)
6. Scarce response to steroids: neutrophilic, eosinophilic, obesity—airflow obstruction [1]

In cases of severe asthma, different clinical pictures can be distinguished, conditioned by the phenotype: [1] persistent chronic symptoms, [2] recurrent severe asthma exacerbations, [3] persistent airflow obstruction, and [4] brittle asthma: type 1 (persistent wild swing in peak flow) and type 2 (sudden acute deteriorations). In some of these variants, the aforementioned viruses (RSV) may be responsible.

One of the main problems at this age in the no compliance of medication. This feeling of well-being makes the adolescent to stop it, using the drugs only when not feeling well and, frequently, in an uncontrolled way and not using the proper medication. Mortality in teenager asthma has been related to self-management of severe crisis, with insufficient or inappropriate medication.

6. Resulting processes

Summarizing the concepts presented, the coordination of the endotype and the phenotype are the basis for the establishment of these currently accepted tracheobronchial processes:

1. Transient early wheezing: no family or analytical history of atopy; early onset and disappearance between 3 and 5 years; decreased lung function, but recovered before 6 years of age; no bronchial hyperreactivity (normal methacholine test); and eosinophilia or high levels of IgE. Possible predispositions: prematurity, genetic (congenital reduction of functional residual capacity (V_{max} FRC)), or environmental (smoking mother, irritants).
2. Non-atopic wheezing: beginning before 3 years of age, the majority (73% of cases) after viral infections (RSV, para-influenza, others), although infection by RSV before 3 years of age has been associated with the risk of persisting wheezing episode till 10 years of age. In general, there is no family history of atopy or clinical or analytical signs of it in the same patient: decreased lung function after infection and progressive normalization with maximum persistence of the process up to 13 years of age.
3. Atopic wheezing/asthma: in which there is no lack of familial atopic predisposition, it starts before 6 years (80%); early sensitization to pneumo-allergens; positive specific IgE and skin tests; frequent coincidence with associated allergic processes (rhinitis, eczema, urticaria); progressive deterioration of lung function and bronchial hyperreactivity; persistence that may reach adulthood, if adequate treatment is not carried out at an early stage (especially immunotherapy when indicated, anti-inflammatory, bronchodilators); and environmental measures [4, 20–23].

7. Controversies

Despite the evidence of the different ways of presenting the bronchospastic processes in the pediatric age, the evidence of the aforementioned predisposing factors has been questioned because there are several respiratory processes with similar symptoms but varying in the age of onset, persistence, family history, and coexistence or not with other processes of allergic cause (cutaneous, digestive). Likewise, the different coincidence of wheezing, atopy, or AHR can condition the different respiratory processes, based on the different uses of the term phenotype, such as:

1. Any observable trait (partial phenotype) includes signs, symptoms, measurements, and biological markers.
2. Clinically useful grouping defines groups that differ with respect to features of interest, e.g., risk factors, response to treatment, and prognosis.
3. Hypothesized disease entity defines a condition that is thought to represent a distinct disease entity.

These factors are the basis for doubting the reality of the phenotypes whose definition is also debatable, requiring a better definition of the term and its possible relationship with the aforementioned respiratory processes. “In the meantime, we should treat phenotypes as exactly that the best current working hypothesis” how the authors of the work finish [24].

Author details

Francisco Muñoz-López

Address all correspondence to: 5314fml@comb.cat

Department of Pediatric Immunoallergology, Faculty of Medicine, University of Barcelona, Clínic Hospital-Sant Joan de Déu Hospital, Spain

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Chapter 4

Functional Lung Examination in Diagnostics of Asthma and Its Phenotypes

Frantisek Lopot, Vaclav Koucky, Daniel Hadraba,
David Skalicky and Karel Jelen

Additional information is available at the end of the chapter

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Abstract

In this chapter, we review the diagnostic approach to asthma phenotypes in children using lung function testing. Various methods are reviewed and their advantages and disadvantages are discussed. Medical history and physical examination including lung auscultation is the first line examination, which may raise the suspicion on asthma. Besides the simple lung auscultation, more advanced approaches (computer analysis of breath sounds) are described. Spirometry and other classical lung function testing methods (body plethysmography, dilution techniques) are discussed with respect to their contribution to asthma diagnostics and phenotype classification. Afterward, impulse oscillometry and methods intended for patients with insufficient cooperation follows. We highlight their potential in diagnostics of early asthma stages. Measurement of exhaled nitric oxide is discussed and its potential for allergic asthma (eosinophilic inflammation) detection is assessed. In conclusion, various lung function testing methods may contribute to both setting the diagnosis of asthma itself and classification of asthma phenotypes. Their smart combination allows for more precise diagnostics and treatment of young patient with bronchial asthma.

Keywords: asthma in children, wheezing, diagnostics, phenotype, endotype classification, lung function testing, spirometry, impulse oscillometry, FeNO, lung auscultation, harmonic analysis, Fourier transform

1. Asthma phenotypes and endotypes in children

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest

tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation [1]. Currently, asthma is considered to be a syndrome rather than one disease with common etiopathogenesis. There have been various attempts to subclassify asthma into more homogeneous groups with similar pathophysiology and clinical presentation. Such subclassification will help to improve the therapeutic approach to our patients and will offer a possibility of individualized therapy, which will increase the safety and efficacy of asthma treatment. Moreover, research in more homogeneous groups of patient will offer better insight into the pathogenesis of bronchial asthma with.

Recently, the terms asthma phenotype and endotype have been introduced. "Phenotype" is defined as a recognizable cluster of demographic, etiologic, and clinical characteristics. These are generally regarded to arise from interactions between the genotype and environmental influences. It may be described by clinical characteristics including physical, biochemical, and other variables that can be objectively measured. There is no reference to an underlying pathophysiological process. The term "endotype" is used to describe a disease subtype based on distinct pathological mechanisms [2].

A number of phenotypes and endotypes in children have been proposed, unfortunately up to now, there is no clear consensus in this field. Martinez et al. categorized wheezing during the first 6 years of childhood into three distinct groups—transient early, persistent, and late-onset wheeze. This classification is based on the presence or absence of wheezing before the age of 3 years and its persistence or incidence to age 6 years. The limitation of this approach comes from the fact that it can be set only retrospectively and thus it is of little clinical impact. Later, another classification of early wheeze has been suggested by a European Respiratory Society task force—a dichotomy based on trigger factors: episodic viral wheeze and multiple-trigger wheeze [3]. Besides the time- and symptom-based approaches, there exist many other phenotypes, which have been adopted from adults: allergic asthma, nonallergic asthma, asthma with fixed airflow limitation, asthma with obesity, and so on. They have some importance in older children (adolescents).

Although phenotype- and endotype-based approaches to asthma are of an extreme importance for research purposes and for understanding asthma itself, to date, no strong relationship has been found between specific pathological features and particular clinical patterns or treatment responses. More research is needed to understand the clinical utility of phenotypic classification in asthma.

2. Functional lung examination in asthma diagnostics

Setting a diagnosis of asthma is difficult and requires a complex approach. There exists no single test capable of setting the diagnosis without other concomitant examinations. Particular difficulties occur when conducting a confident diagnosis in children younger than 5 years. Symptoms of cough and wheeze are very common in this age and the assessment of airflow limitation is also age-restricted, all leading to difficulties with setting up the diagnosis. A probability-based approach, based on the pattern of symptoms during and between viral

respiratory infections, may be helpful [1]. It allows to individually decide about the trial of controller treatment (usually inhaled corticosteroids—ICS), which may further underpin the diagnosis.

Besides the evaluation of clinical symptoms (wheeze, cough, breathlessness, activity, and social behaviour), adjunct tests may be employed as well [1]. Because of the scope of our chapter, we focus on lung function testing and exhaled nitric oxide levels.

The evaluation of airflow limitation and its reversibility is a key question in asthma-diagnostic approach. However, it must be noted that the presence of airflow limitation (even reversible after beta-agonists) does not confirm the diagnosis. Other aspects need to be taken into account when making conclusions. All the limitations of the functional examination may be deduced from this fact. A similar situation occurs in phenotype classification. In case of time-based classification of wheezing phenotypes, the early functional lung examination may assist to objectify the presence of airflow limitation and its development in time. In case of symptom-based classification, the functional examination is of smaller importance; however, it may assist in clinically uncertain situations. Endotype classification is usually based on invasive tests (e.g. endobronchial biopsies, bronchoalveolar lavage cytology, etc.). However, some tests such as exhaled nitric oxide measurement may indicate the allergic (eosinophilic) asthma endotype. To sum up, functional examination informs about the presence of airflow limitation and its reversibility, but with the exception of fractional exhaled nitric oxide (FeNO), it will only assist in phenotype classification.

3. Evaluation of bronchial obstruction by different lung function-testing methods

In this subchapter, various methods for detection of bronchial obstruction will be reviewed. We focus on tests that are routinely used in clinical settings. In addition, we discuss less available methods, which have the potential to enrich the spectrum of diagnostic tools in future. However, their clinical impact needs to be further studied.

The choice of diagnostic tool is influenced by several factors:

- sensitivity of the method with regard to bronchial obstruction, respectively asthma itself,
- specificity of the method with regard to bronchial obstruction, respectively asthma itself,
- invasiveness of the method and patient burden (e.g., need of sedation/anesthesia, radiation, etc.),
- age of the patient—depending on the ability of the child to follow up the instructions and coordinate breathing, some methods (e.g., spirometry) are available only in older children,
- availability of the method,
- time and financial demands.

When indicating an optimal diagnostic test, one should bear in mind its different characteristics and potential limitations in asthma diagnostics and phenotype classification. In a clinical setting, a combination of several methods is employed to reach a confident diagnosis.

3.1. Lung auscultation

Because of its simplicity, noninvasiveness, and wide applicability, lung auscultation is the first-line method in lung examination. This method is a part of the physical examination and is usually accompanied by aspection, palpation, and percussion. The subject of the examination is the sound effect of the air flow passing from and to the alveoli. A sit does not require special patient cooperation. This method can be applied to the whole-age spectrum of the patients. On the other hand, it has also several disadvantages. Taking the principle of the method into account, it is not possible to completely eliminate the contamination of the tracked sound signal by artifacts from the internal and external surroundings of the patient. Those signal artifacts may be of such intensity that important information gets lost. Moreover, the sensitivity of lung auscultation in the detection of bronchial obstruction is relatively low. The bronchial obstruction is not reliably recognizable if the airway lumen is reduced less than by 30–50% as compared to the healthy state. These problems can be solved in part by appropriate frequency tuning of the phonendoscope, or by processing the captured record by one of the advanced audio signal-processing methods—see subsequent subchapter. The first-mentioned adjustment is applicable in general but has only a limited effect with respect to the range of commonly observed frequencies. The second adjustment is bound to the possibility of making any record of the listening examination. Several phonendoscopes, which enable to make audio recordings, are currently available on the market. These recordings can then be played back and processed using specific software on a common PC.

Another disadvantage of lung auscultation is the considerable level of subjectivity in its evaluation. The Working Group of the European Respiratory Society and the American Thoracic Society (ERS/ATS task force) drew up a paper on the standardization of the lung sound nomenclature [4]. A library of reference auscultation findings has been created, including their interpretation [5]. Typical findings for bronchial obstruction include "wheezing" and non-constantly "prolonged expiration" (i.e., expiration phase more than two times longer than inspiration). The finding of these sound phenomena indicates the presence of bronchial obstruction with a high probability and is an indication for the beta-mimetic therapeutic test (salbutamol/albuterol). Positivity of this therapeutic test further supports the diagnosis of bronchial obstruction and indicates its reversibility. In order to obtain valid results of this test, several rules need to be followed—the application of sufficient dose of beta-mimetic (400 mg of salbutamol in the form of a "metered dose inhaler"), the correct way of application—via a "spacer" ("aerochamber"), and last but not the least, sufficient interval between the applications of beta-mimetics and the lung auscultation (15–20 min).

To conclude, lung auscultation and the detection of obstructive phenomena (wheezing, prolonged expiration) together with positive beta-mimetic test are the basic and most available diagnostic tools for bronchial obstruction.

3.2. Spirometry

Spirometry is a test that measures how an individual inhales or exhales volumes of air as a function of time. The primary signal measured in spirometry may be volume or flow. Spirometry is highly valuable as a screening test of general respiratory health. However, on its own, spirometry does not lead clinicians directly to an etiological diagnosis. Spirometry requires cooperation between the subject and the examiner, and the results obtained will depend on technical as well as personal factors. In children, the spirometry is recommended to be performed from the age of 3–5 years depending on the child's psychomotor development (ability to follow instructions and coordinate breathing) and experiences and skills of the examiner. Naturally, the success rate of spirometry in the preschoolers is much lower than in older children.

During spirometry, several maneuvers may be performed, which will answer various clinical questions:

- forced vital capacity (FVC) and forced expiratory volume in 1-s (FEV1);maneuver—derivation of maximum effort flow-volume curve;
- slow vital capacity (sVC) and inspiratory capacity (IC) maneuver;
- peak expiratory flow (PEF);
- maximum voluntary ventilation (MVV).

Details of the previously mentioned examinations may be found in ERS/ATS document [6]. Technical demands for the devices, guidelines for quality control and reporting may be found also in previously mentioned ATS/ERS document.

3.2.1. Diagnostic use of results

In principle, there are two main types of lung diseases, the so-called obstructive and restrictive ones. Both types lead to changes in ventilation and are reflected by specific spirometric parameters.

Figure 1 shows the usual shape of the expiratory limb of the maximum effort flow-volume curve (MEFV) as well as the physiologic time-volume tracing found in healthy individuals.

In case of a restrictive disorder, the velocity of expiration is usually normal, but there is a reduction in pulmonary volumes (**Figure 2**). Both the FVC and FEV1 parameters are reduced, and their reduction is proportional leading to normal FEV1/FVC index (the so-called Tiffeneau index is within the norm for the patient's age).

Contrarily, the obstructive disorder (**Figure 3**) is characterized by a decreased expiratory velocity, and lung volumes are usually preserved. In case of severe or complicated obstruction, air trapping and hyperinflation may occur, both leading to a secondary decrease in FVC. The typical finding of obstructive ventilation disorder is therefore a reduced FEV1, FVC is normal or decreased disproportionately to FEV1, resulting in a reduction of the Tiffeneau index mentioned earlier.

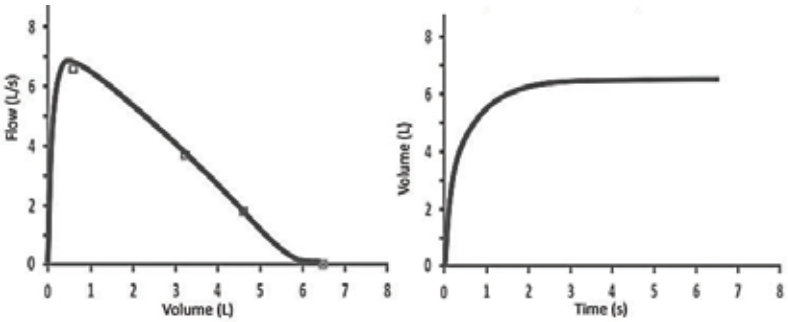

Figure 1. Typical shapes and values of breathing curves (taken from [7]).

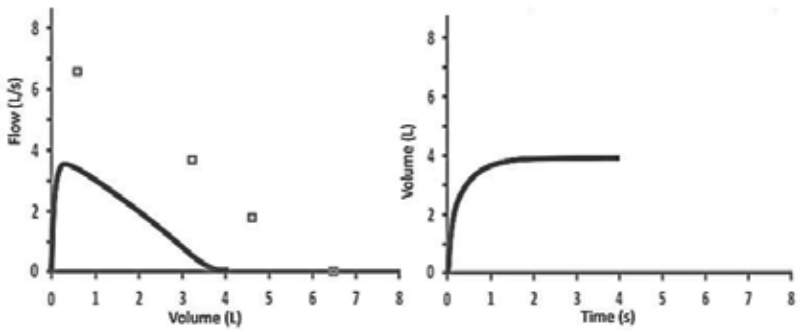

Figure 2. The effect of restriction disorder (taken from [7]).

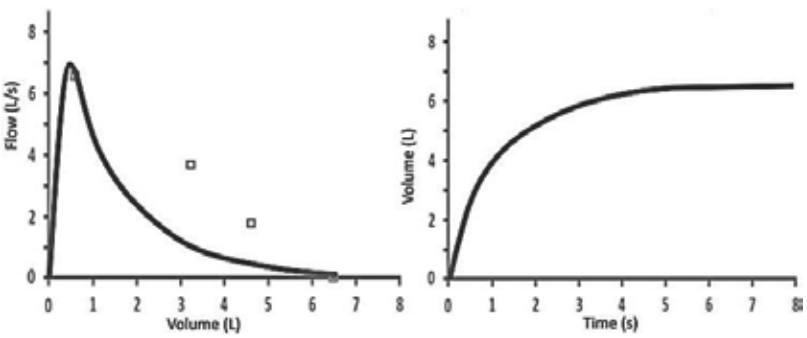

Figure 3. The effect of obstructive disorder (taken from [7]).

When interpreting the spirometry results, one should bear in mind that the complete assessment of pulmonary volumes is possible only using body plethysmography (or dilution techniques). After that, obstructive and restrictive ventilation disorders can be reliably distinguished. The optimal lung function interpretation strategy proposed by ATS/ERS task force is shown in **Figure 4**.

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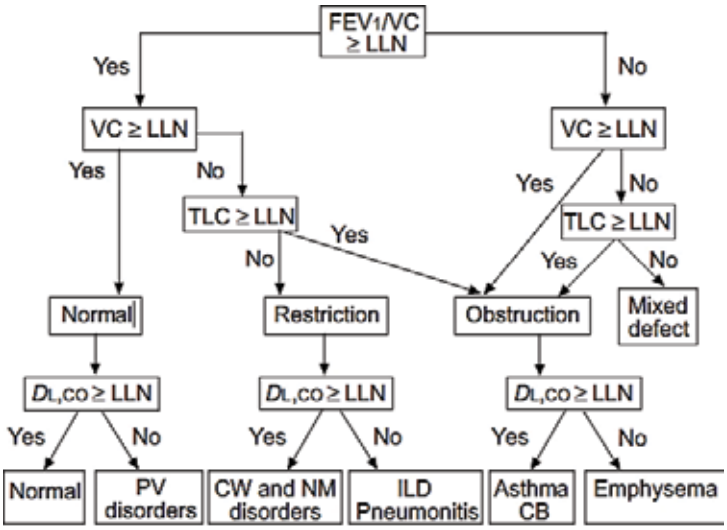

Figure 4. Algorithm for diagnostic evaluation of spirometry (taken from [8]). VC, vital capacity; LLN, lower limits of normal; FEV1, expiratory volume in 1 s; TLC, total lung capacity; $D_{L,CO}$, diffusing capacity for carbon monoxide; CW, chest wall; NM, neuromuscular; ILD, interstitial lung diseases; CB, chronic bronchitis.

As mentioned earlier, the information obtained from the simple spirometry is sufficient to raise only suspicion on the disease. The final diagnosis always needs to be confirmed by other methods (see subsequent subchapters) or by spirometry performed under specific conditions —the so-called bronchomotoric tests. They include bronchodilating test—that is, evaluation of airway obstruction after bronchodilator administration—usually beta-2-mimetics. If bronchial hyperresponsiveness needs to be evaluated, bronchoconstrictive test with direct or indirect stimuli capable of induction of bronchospasm may be used. The most commonly used bronchoprovocative stimuli include methacholine, histamine, mannitol, dry and cold cough, or physical activity.

3.3. Whole-body plethysmography

According to the definition, the whole-body plethysmography is a diagnostic method based on the measurement of volume changes of the patient's body during respiration. Applied to pulmonary function testing, it allows to determine the total pulmonary capacity (TLC) and all its components including indirectly measurable volumes. Similar to the spirometry, the results are significantly affected by conditions of measurement and their history before it. That is why it is generally not allowed to smoke, to eat heavy foods, to drink alcohol, to have an excessive physical activity, and so on, before this examination. The examination takes place in an airtight box. The patient stands or sits inside and breathes through the mouthpiece and the nose is closed by a pin. The examination proceeds in two phases (specific airway resistance measurement—performed with opened shutter and FRC measurement—inspiration and expiration against the closed shutter). A schematic derivation of the respective parameters is shown in **Figure 5**.

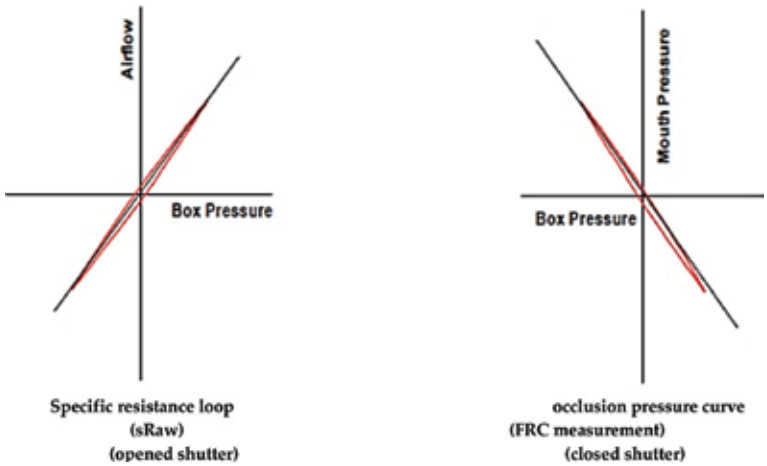

Figure 5. Output curves of plethysmography (taken from [9]).

3.3.1. Diagnostic use of results

As mentioned earlier, body plethysmography allows the evaluation of indirectly measurable pulmonary volumes and capacities—that is, residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC). They allow conducting a definitive diagnosis of restrictive lung disorder. In addition, it is possible to assess respiratory tract resistance (Raw) —important for airway obstruction assessment.

The quantification of the given parameter is performed using the inclination of the given curve/loop. The shape of specific resistance loop is also of a significant diagnostic value—it can indicate the localization of the obstruction within air passages (**Figure 6**).

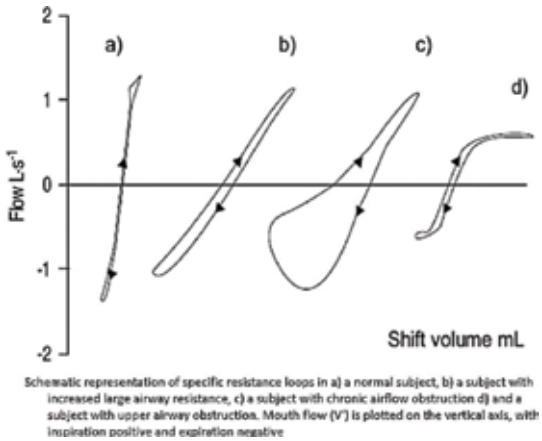

Figure 6. Typical shapes of specific resistance loops (taken from [9]). Note: the pressure in the box on the horizontal axis is replaced by the corresponding volume change of the air in the box.

Figure 7 shows a typical finding in a healthy individual, a patient with obstructive and restrictive disorder, respectively.

3.4. Dilution techniques

Dilution techniques represent complementary method to the abovementioned functional examinations. Similar to the body plethysmography, they enable to evaluate indirectly measured volumes and pulmonary capacities (RV, FRC, and TLC). In principle, two modifications of this method are available—the closed variant using Fick's principle and the opened method (e.g., multiple-breath inert gas washout test). In the diagnostics of bronchial obstruction and asthma, these methods give only complementary information.

3.5. Impulse oscillometry

Impulse oscillometry (IOS) is one of the modifications of forced oscillation techniques (FOTs). It is a noninvasive diagnostic method which is performed during tidal breathing and is based on the superimposition of external pressure signals on the patient's tidal breathing. In a simplified way, we can say that the whole respiratory tract including air in the airway is forced by external pulses of different course in time to oscillate. The behaviour of the respiratory tract is then described by several variables (resistance, reactance, inertance, and elastance) which allow assessing mechanical properties of the respiratory tract and its components (airways, lung parenchyma, and chest wall). To get reliable results, it is necessary only to ensure a regular breath pattern (no specific breathing maneuvers are required). The examination can thus be performed in all age categories of patients.

The following parameters are evaluated when interpreting IOS results:

- respiratory tract resistance (R_{rs}) and its frequency dependence,
- respiratory tract reactivity (X_{rs}) and its frequency dependence,
- auxiliary parameters (resonant frequency—F_{res}, volume dependence of Z_{rs} impedance, and others).

The outcome of the examination gives information about the resistance of the central and peripheral airways. Further, it also gives an overview of the mechanical properties of the respiratory tract. It should be noted that basic IOS examination (i.e., without specific breathing maneuvers) does not provide any information on lung volumes.

In conclusion, IOS is a suitable method for the diagnostics of bronchial obstruction in noncooperative and poorly cooperative patients.

3.6. Fractional exhaled nitric oxide (FeNO)

Measuring the fraction of nitric oxide in exhaled breath is relatively new and promising tool assisting conventional lung function testing in asthma diagnostics and phenol/endotype classification. Nitric oxide is an important mediator with plenty of different functions; when

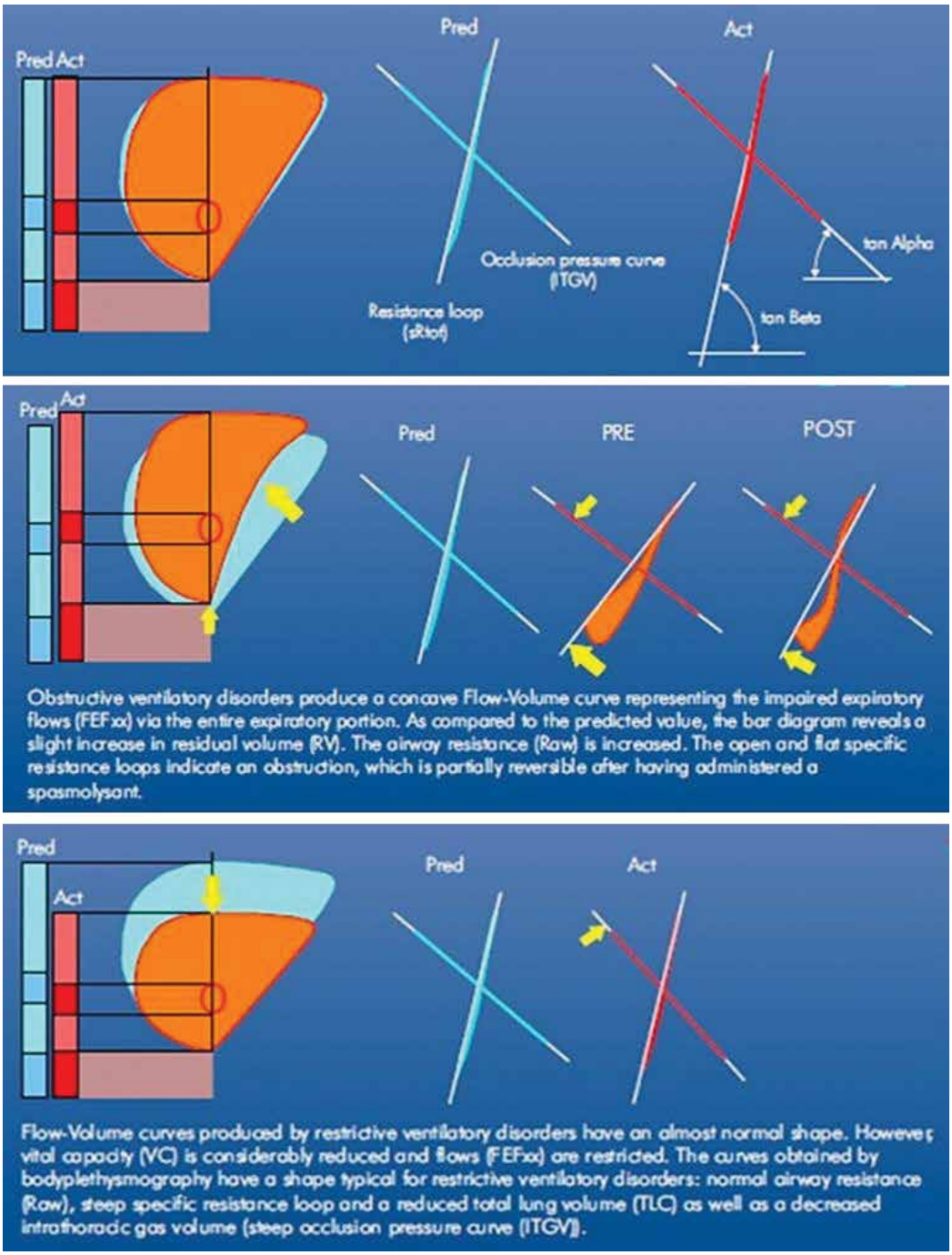

Figure 7. Typical shapes of spirometric and plethysmographic curves (taken from [9]). Note: "Pred" means predicted and "Act" means actual value or shape of the followed-up parameter.

assessed in exhaled air, it reflects the allergic airway disease, more precisely the activity of eosinophilic inflammation. While symptoms and lung function assess the pathogenetical mechanisms of allergic asthma indirectly, FeNO measurement reflects directly the activity of this inflammation. It is strongly and positively correlated with eosinophils in airway wall, bronchoalveolar lavage fluid, and induced sputum. As a noninvasive tool, it may greatly contribute to the diagnostics of allergic/eosinophilic phenotype of asthma [10].

Currently, there exist various modifications of FeNO-measuring systems including online and offline variants. Principally, there exist single- and multiple-breath approaches, both having its advantages and disadvantages. Technical aspects of these methods have been reviewed elsewhere [11]. FeNO measurements may be successfully performed in young children as well [12]. Modifications for infants are also available.

There is sufficient evidence about the usefulness of FeNO in clinical setting—especially in patients with asthma. FeNO measurements are highly correlated with eosinophilic airway inflammation, and as this type of inflammation positively responds to steroid treatment, it can guide the therapy. High levels of FeNO predict steroid responsiveness. Moreover, it can predict the relapse of asthma symptoms after steroid treatment withdrawal [13].

To conclude, we highlight the role of FeNO measurement in both asthma diagnostics and phenol/endotype classification. It may be regarded as an "inflamometer," as though this tool should be available to the pulmonologist managing asthma patients.

3.7. Lung function testing in infants, toddlers, and preschoolers

According to GINA 2017 [1], lung function testing (spirometry) is recommended for patients older than 4–5 years when setting the diagnosis of asthma and for long-time follow-up. As children younger than 3–4 years are usually not capable of performing acceptable trials of maximum effort flow-volume curve, alternative methods are used to objectify their lung function. These methods (infant pulmonary function testing—IPF) are not widely available, and their clinical impact remains unclear [14, 15]. However, based on the authors' experiences, IPF may be of a clinical benefit in the management of infants with recurrent wheeze.

Currently, there exist a number of commercially available methods assessing different aspects of lung function (**Table 1**). These methods require tidal breathing and face-mask tolerance; consequently, they are performed under light sedation (chloral hydrate). Generally, they are considered to be safe and well tolerated. Principally, it is also possible to perform bronchomotoric test in infants using various methods of IPF. Their limitations include the need of prolonged sedation (at least 30 min of quite sleep) to conclude the subsequent testing, various technical problems (no commercially available equipment for such testing), and the need of knowledge of the short-term variability of the respective parameters. In author's lung function laboratory, bronchodilator test with salbutamol is routinely performed with valuable clinical implications. To our knowledge, there is no laboratory performing bronchoconstrictive tests in infants on regular basis.

Method	Outcome	Parameter
1. Bodypletysmography	Lung volume	Functional residual capacity (FRC)
	Central airway obstruction	Airway resistance (Reff)
2. TidalBreathAnalysis	Ventilation	Minute ventilation
	Peripheral airway obstruction	Shape of the FV curve, tPTEF/tE
3. Resistance-Compliance	Mechanic properties of respiratory tract	Compliance (Crs)
		Resistance (Rrs)
4. Thoracoabdominal compression	Peripheral airway obstruction	Maximal flow at the FRC level
	Ventilatory reserve, airway collapse	Shape of the FV curve
5. Raised volume thoracoabdominal compression	Additionally to 4.: Lung volumes	Total lung capacity (TLC), vital capacity (VC)
6. Multiple breath washout test	Lung volume	Functional residual capacity (FRC)
	Ventilation inhomogeneity (most peripheral airway obstruction)	Lung clearance index (LCI)

Table 1. Summary of lung function methods intended for patients with limited cooperation and their outcome parameters.

The contribution of IPF in asthma diagnostics includes the detection of airway obstruction, its localization (peripheral or central airways), its quantification (mild, moderate, and severe) and reversibility (reaction on salbutamol). In addition, consequences of bronchial obstruction such as hyperinflation, ventilation inhomogeneity, and changes in breathing pattern may be detected as well.

4. Utilization of advanced methods for processing of audio signals

Together with the development of possibilities and availability of computer technology, the possibilities of using exact computational methods of signal processing grow both in basic research and in the field of practical problems. From a number of methods available, we prefer the harmonic analysis. The outcomes of all available methods are similar likely due to the demand for easy interpretation of results to physicians or patients. We describe the given approach on the basis of the Fourier transform analysis, where we have achieved the most convincing results so far.

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4.1. Background

The validity and reliability of outputs of the advanced sound analysis significantly increases with the quality of the input data. It is also advantageous to know what frequencies are important to look for and what their presence means from both diagnostic and technical point of view.

The most specific issue is created by pediatric patients, where the quality of respiratory sound can also be affected by the size of the patient body. Children have a distinct quality of lung sounds, which is generally attributed to acoustic transmission through smaller lungs and thinner chest walls. Acoustic measurements have shown higher median frequencies of normal lung sounds in infants than in older children and adults [16]. Scientific studies show that higher median frequencies in infants were explained by lower power at low frequencies, while the decrease in power toward higher frequencies was similar at all ages (infants, children, and adults) [17].

4.2. Physical principle of sound in the airways

The harmonic analysis is a mathematical apparatus for processing the oscillating periodic signal, which the sound also is. Sound is an oscillation of acoustic pressure, which propagates by space. The oscillation of acoustic pressure is composed of many sine oscillations characterized by various frequencies. A timbre and character of sound detectable by human ear originates from the number of oscillated frequencies. The sound composed of the integer multiples of the base frequency (the lowest frequency) with a clearly defined period is perceived as a musical tone. On the contrary, the sound including the noninteger multiples of the base frequency and without a clearly defined period is perceived as noise [18].

The respiratory sound, which is caused by airflow in airways, is sound in a frequency range from 20 to 2000 Hz and higher. However, it can still be detected at or above 2000 Hz with proper sensitive microphones in a quiet room according to our experience [16, 17, 19]. The normal lung sound spectrum is devoid of discrete peaks and is not musical [18].

One of the manifestations of asthma and other respiratory diseases is bronchial obstruction. Such a narrowing of the air passages causes a vibration and turbulence of the airflow, which results in the change of the sound manifestation of breath. This change of sound, which is manifested by the presence of wheezing and crackles, can be detected by listening using the phonendoscope. For wheezing, the frequencies in the range of 300–1000 Hz with higher amplitudes in comparison with neighboring areas are typical [20]. The duration of these areas is normally from 0.5 to 0.75 s. These searched phenomena in the respiratory sound could be emphasized using an intensive respiration caused, for example, by physical activity [20–23].

4.3. Harmonic analysis and Fourier transform

Using harmonic analysis, such a sound can be decomposed and particular frequencies of mentioned sine oscillation can be searched. Thus, the important frequencies of wheezes can

be discovered too. The visualized result of the Fourier transform is called the frequency spectrum [18] and its example is shown in **Figure 8**.

Figure 8 shows the frequency spectrum of analyzed music sound in a defined time range—the horizontal axis is a frequency scale and it indicates harmonic frequencies in this sound; the vertical axis indicates an amplitude level of every frequency in the sound. The frequencies can be clearly defined in this case because the analyzed sound is a mentioned musical sound.

For illustrative interpretation of the outputs of harmonic analyzes, we have developed our own software. The software operates on the principle of mentioned Fast Fourier Transform using Matlab background and creates frequency spectra throughout the length of the analyzed recording, working with defined time intervals [22]. The length of the time intervals corresponds to the duration of wheezing approximately. For better clarity of outcomes of performed analysis, a specific suitable color scaling for frequencies in the obtained frequency spectra was applied [21, 22]. Then, every level of amplitude is defined by one concrete color (**Figure 9**).

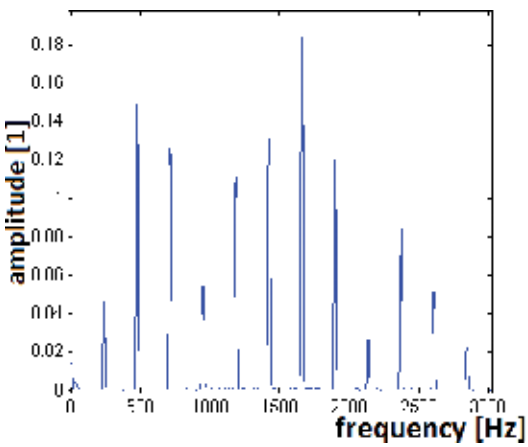

Figure 8. Illustration of frequency spectrum.

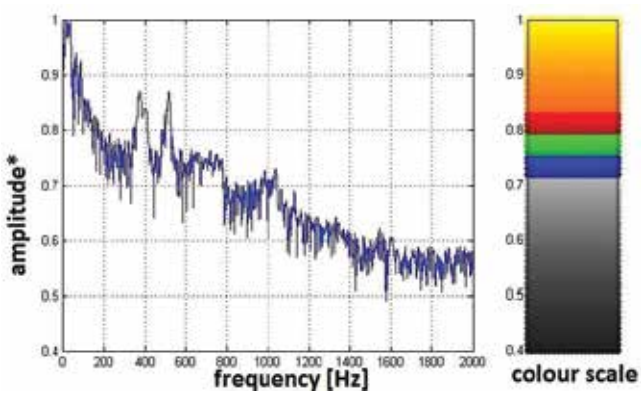

Figure 9. Color scaling of obtained frequencies. The color scale matches special colors according to values of all amplitudes.

Finally, the colored data were rearranged back to the time line of original recording (**Figure 10**).

By this approach, the oscillations of acoustic pressure are presented by the progression of the frequency spectra of the sound recording in time (**Figure 10**). Such a method of sound-recording acquisition of patients' breath, which is required for frequency spectrum creation and for the detection of wheezing in this spectrum, is completely noninvasive and without the need of cooperation of patient.

4.4. Our experimental work

While looking for a way of how to utilize the harmonic analysis in auscultation examinations most effectively, we have performed relatively large set of experiments. The main part of the work includes data collection. Based on these data, we have verified and modified the properties of our method to best suit our purpose. All audio recordings of respiratory sounds were obtained in collaboration with the Department of Pneumology in UH Motol.

The following text is focused on the part of our study, which was attended by nine volunteer patients with asthma aged from 9 to 18 years. It is a relatively homogeneous group in terms of diagnosis and clinical manifestations. In this group, it was also possible to perform the generally respected spirometric examination for subsequent result comparison.

4.4.1. Instrumentation

The usual commercially available electronic phonendoscope Littmann 3200 recording the heard respiratory sound was utilized in the study. The instrument digitizes the recording with a sampling frequency of 4000 Hz and allows the application of a specific input filtration. The

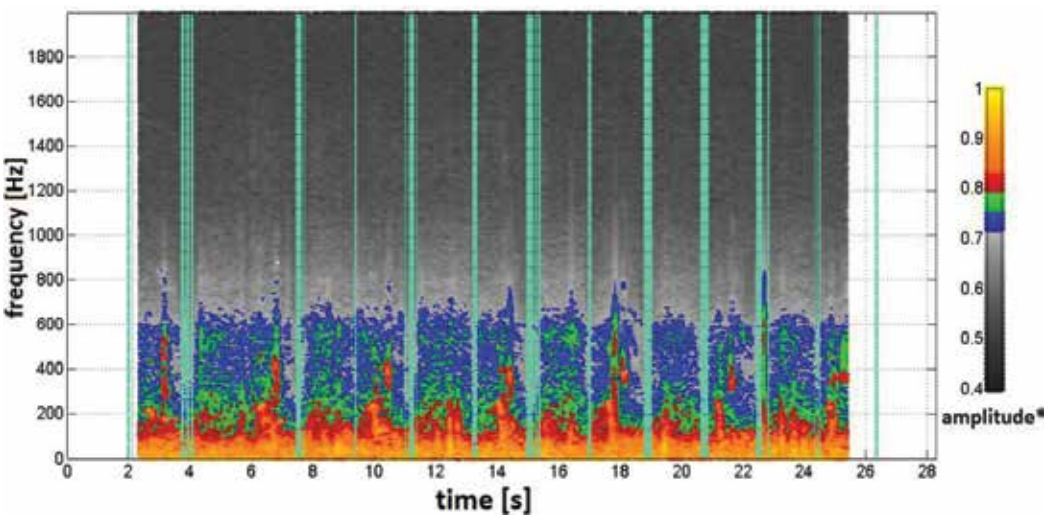

Figure 10. The frequency spectrum of sound recording of patient's breath. The pale blue vertical lines indicate moment of transitions between inspiration and expiration phase. The lines repeat in 2-s time interval. It corresponds to the length of respiratory cycle (inspiration + expiration) for ordinary human in defined age [21].

manufacturer does not provide any information about the sensitivity of the device, but guarantees that the limiting factor in the evaluation of the recordings will always be the auditory organ of the listener and not the sensitivity of the instrument.

4.4.2. Measurement protocol

The quality of respiratory sound recording is affected by location, where the sound was recorded [20, 22–24]. Probably, the best location for respiratory sound recording is on the back on paravertebral line on the right and left side (lung lobes in **Figure 11a** and **b**) and on jugulum (**Figure 11c**). The sound with frequencies up to 600 Hz goes through lung parenchyma better than the sound with frequencies over 600 Hz. These frequencies could be detected better on jugulum.

The recordings were acquired in the examination of patients during restful and deep breathing, which was induced by light physical load (10–15 squats) according to instructions and under the supervision of the attending physician.

4.5. Results

Data processing followed the procedure described in Chapter 4.3. In all patients included in our study, specific artifacts (**Figure 12**, black-circled areas) appeared in the expiration phases. In two of those cases, these artifacts were not listened by experienced physicians just as a result of their extinction within the other recorded noise. Data processed so far indicated that in asthmatic patients, there are clearly visible manifestations of the obstruction in the expiration phases in the frequency ranging from approximately 400 to 600 Hz, regardless of whether they are identifiable by listening or only through our analysis.

Even the control records of healthy volunteers are not without interest. From **Figure 13**, it is well seen that they show significantly lower level of noise compared to the asthmatic patients in all of the breathing phases.

It is worth noting that there are vertical pale blue lines indicating the transitions between inspiration and expiration. These lines were also determined automatically by applying a harmonic analysis with the use of the fact that the airflow stops at that moment [21].

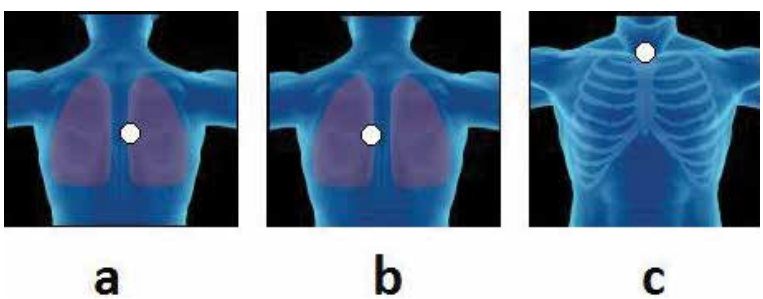

Figure 11. Locations for sound recording.

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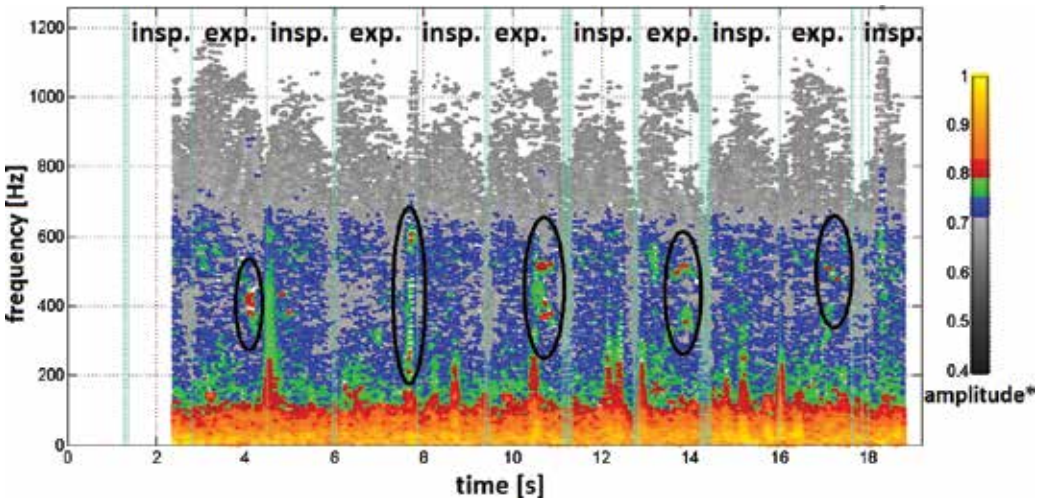

Figure 12. Development of amplitude and frequency spectrum of an asthmatic patient.

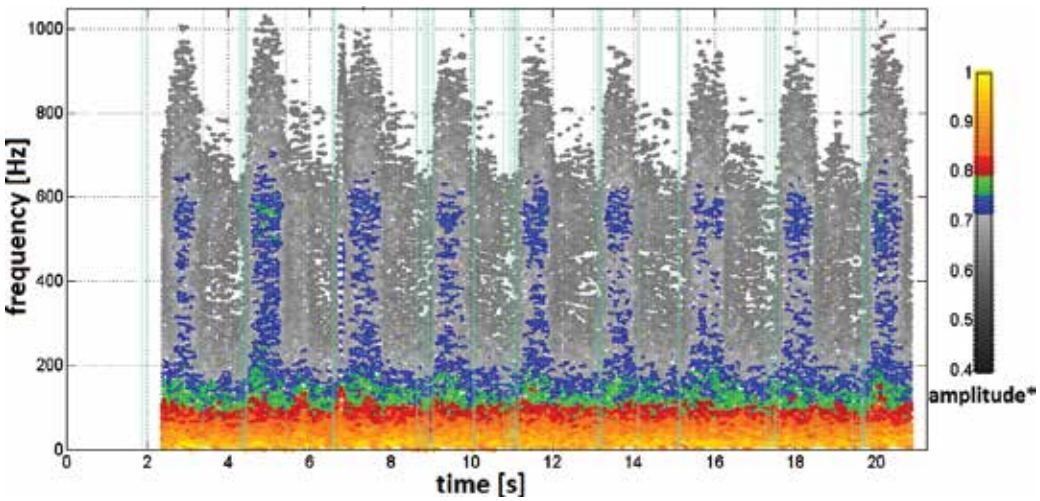

Figure 13. Development of amplitude and frequency spectrum of a healthy volunteer.

5. Conclusion

Data processed so far show that—despite the relatively simple technique used—the audio display provides valuable diagnostic information. Furthermore, using a suitable method, this information can easily be detected in the record through specific sound phenomena despite other sounds in the record. Therefore, we believe that research focused on alternative complementary methods has its importance—it can provide solutions in cases where other commonly observed methods fail or are complicated to be applied.

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Author details

Frantisek Lopot[1,4], Vaclav Koucky[2,4], Daniel Hadraba[1,3,4], David Skalicky[1,4]* and Karel Jelen[1,4]

*Address all correspondence to: skalickydavid@seznam.cz

1 Department of Anatomy and Biomechanics, Faculty of Sports and Physical Education, Charles University, Praha, Czech Republic

2 Second Faculty of Medicine, Charles University, Praha, Czech Republic

3 Department of Paediatrics, University Hospital Motol, Praha, Czech Republic

4 Department of Biomathematics, Institute of Physiology, Czech Academy of Sciences, Praha, Czech Republic

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Chapter 5

Asthma in the Disadvantaged: A Phenotype in Need of a Personalized, Multidisciplinary Approach to Therapy

Drew A. Harris, Caitlin Welch, Morgan Soper and Yun Michael Shim

Additional information is available at the end of the chapter

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Abstract

Most patients with asthma can be managed with standardized, traditional therapies; however, 5–10% of patients suffer from disease that is difficult to control. Uncontrolled asthma disproportionally affects low income and racial minority patients. The disadvantaged asthma phenotype is defined by the presence of overlapping social, economic and environmental factors. These factors, such as environmental exposures in substandard housing or suboptimal adherence to controller therapy due to impaired health literacy are challenging to address in the clinic or inpatient setting. Personalized management of the disadvantaged asthma phenotype must target these interconnected factors through a multidisciplinary approach that includes longitudinal collaboration with community-based organizations, social workers and legal aid.

Keywords: asthma phenotypes, vulnerable populations, asthma disparities, health equity, social determinants of health

1. Introduction

1.1. Health disparities in asthma

Asthma is a heterogeneous clinical syndrome centered on symptoms of dyspnea, cough, wheezing or chest tightness, along with reversible expiratory airway obstruction or bronchial hyperresponsiveness. Although asthma affects 5–10% of the world's population, asthma disproportionally impacts communities of color and the socioeconomically disadvantaged.

In adults, asthma is more common in non-Hispanic blacks (8.7%) and Puerto Ricans (13.3%) than in whites (7.6%), and asthma-specific mortality is significantly higher in non-Hispanic blacks (25.4 per million, annually) compared to whites (8.8 per million, annually) [1]. In children, the prevalence of asthma is much higher in Puerto Rican Hispanics (19.2%) and non-Hispanic blacks (12.7%) than in whites (8%) or Mexican Americans (6.4%) [2]. Asthma-specific mortality in children is nearly eight times higher in non-Hispanic blacks than in whites [3]. In addition to racial disparities, socioeconomic disparities in asthma outcomes are widespread, with socioeconomically disadvantaged asthmatics less likely to utilize preventative care for asthma and more likely to rely on urgent and emergent health care for asthma [4]. Asthma outcomes are substantially worse for racial minorities with lower socioeconomic status [5].

1.2. The disadvantaged asthma phenotype

The term "asthma" envelops multiple phenotypes of disease. A phenotype is defined by the observable properties produced by the interactions of a genotype and the environment. In recent years, multiple asthma phenotypes have been defined by natural history, clinical and physiological features, biology and biomarkers and response to therapy [6]. Specific asthma phenotypes are important to consider in order to identify a targeted, personalized approach to asthma therapies.

1.3. Social and environmental factors relevant in the disadvantaged asthma phenotype

Numerous social and environmental factors can influence the underlying immunologic and inflammatory processes that define an asthma phenotype. In this chapter, we introduce the disadvantaged asthma patient phenotype, defined by specific genetic, socioeconomic and environmental factors commonly experienced by the disadvantaged asthma patient.

Although genetics play an important role in the susceptibility of African American and Puerto Ricans to poor asthma outcomes [7, 8], race and ethnicity are complex social concepts that are informed by genetic, cultural and historical factors [9]. As such, it is challenging to separate genetic factors from social, cultural and environmental factors driving asthma disparities. Racial and ethnic disparities in asthma are likely due to a combination of genetic factors as well as socioeconomic and environmental determinants of health (see **Figure 1**).

These socioeconomic and environmental factors, such as environmental exposures in substandard housing or suboptimal adherence to controller therapy due to impaired health literacy are challenging to address in the clinic or inpatient setting. Personalized management of the disadvantaged asthma phenotype must target these interconnected factors through a multidisciplinary approach that includes longitudinal collaboration with community-based organizations, social workers and legal aid. This chapter will start with a description of specific socioeconomic and environmental challenges most relevant to identify in the disadvantaged asthma phenotype. Following this, recommendations for a multidisciplinary approach to address modifiable factors and improve asthma outcomes in the disadvantaged asthma patient will be presented.

1.4. Indoor allergens in the disadvantaged patient's home

Racial disparities in allergic sensitization are an important contributor to racial disparities in asthma outcomes. Given the epidemic of allergy that has emerged over the last few decades,

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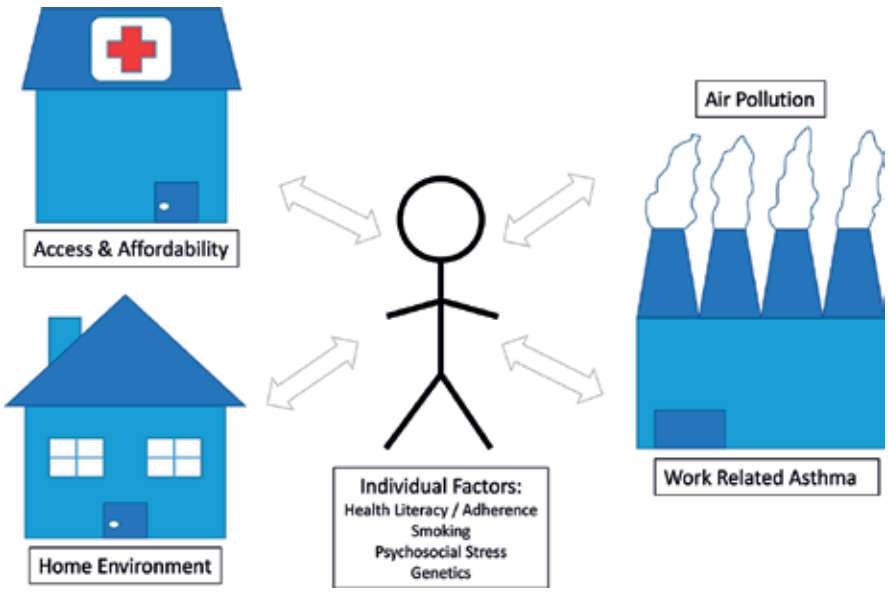

Figure 1. Multiple interconnected factors relevant to the disadvantaged asthma phenotype.

disparities in allergic sensitization are unlikely entirely explained by genetics alone. A combination of environmental exposures and host-susceptibility, such as epigenetic changes and gene-environment interactions, are important mechanisms to consider [10]. Within this context, the home environment is important to consider.

In the US, Black and Hispanic households are more than twice as likely as White households to live in substandard housing [11]. Living in substandard housing leads to increased exposure to indoor allergic asthma triggers such as cockroaches and mice. The increased exposures that racial minorities experience in substandard housing likely contributes to disparities in sensitization [12]. This has been demonstrated in multiple studies including: (1) The National Health and Nutrition Examination Surveys (NHANES) III study of 10,508 individuals, in which non-Hispanic black individuals were more likely than non-Hispanic white individuals to be atopic (62% versus 51.3%, OR = 1.6 95% confidence interval 1.2–1.8) [13]; (2) The Boston Epidemiology of Home Allergens and Asthma study, in which black women were 2.5 times more likely than white women to be sensitized to more than 3 allergens, including dust mite, dog, cat, cockroach, alternaria and aspergillus species [14]; and (3) A study in Hartford Connecticut in which Puerto Rican children with asthma were more likely than white children to be sensitized to indoor allergens such as cockroaches (OR 3.3 95%CI (1.7–6.4) and dust mites (OR 1.7 CI 1.2–2.4) [15].

Sensitization to indoor allergens such as cockroaches [15–17], dust mites [18], animals and the number of positive skin tests to allergens [19] has been associated with increased asthma morbidity and severity. Thus although the interplay between individual genetics and susceptibility to home environmental exposures is not yet fully understood, it is important to consider the exposure to high levels of indoor allergens as well as indoor allergy sensitization in identifying a treatment strategy for patients with a disadvantaged asthma phenotype.

1.5. Considerations for the disadvantaged patient living in a rural environment

Although asthma disparities have traditionally been associated with urban environments, there is increasing recognition that in the US, rural residents suffer from greater poverty and have less medical insurance than those living in urban areas [20]. Rural asthma patients are more likely to have to travel greater distances to travel to health care, which leads to increased asthma morbidity and mortality [21]. Within a month after an emergency room visit for asthma, rural adults are less likely than urban adults to have a follow up office visit for asthma [22]. Given the interconnectedness between poverty, access to care and many of the social and environmental factors discussed in this chapter, it is not surprising that recent evidence suggests that poverty and race, rather than residence in an urban location, are the major risk factors for prevalent asthma [9].

1.6. Work related asthma in the disadvantaged patient

In addition to indoor allergen exposures at home, exposures at work are an important but largely unappreciated determinant of asthma within disadvantaged populations [23]. Work-related asthma occurs in 20–50% of employed asthmatics due to exposures to dusts, fumes, cleaning products, mold, construction debris and temperature extremes [24]. Those who experience work-related asthma are more likely to become unemployed and have lost work time. In the disadvantaged asthma patient, work related asthma can have devastating financial consequences: job insecurity from work-related asthma can lead to worsened asthma measures [25], loss of insurance and healthcare access, and subsequent widened inequities [26]. The economic stress due to the cessation of work or reduced work hours due to asthma symptoms, and subsequent lower incomes can further worsen asthma outcomes [27–31]. Despite the prevalence and importance of work related asthma in disadvantaged populations, work related asthma is often unrecognized by both patients and providers [32].

1.7. Smoking and environmental tobacco smoke in the disadvantaged

Although overall smoking rates of declined in US adults from 20.9% in 2005 to 16.8% in 2014, there remains significant racial and socioeconomic disparities in smoke exposure. Individuals living below poverty (26.3%) smoke more often than those above poverty (15.2%). Households in poverty (36%) are more likely than households above poverty (22%) to have an in-home smoker. African Americans (21.5%), Hispanics (16.2%) and mixed race individuals (24.8%) are much more likely to smoke than Asians (13.3%) or Whites (12.9%) [33].

Cigarette smoking is associated with increased asthma incidence, increased asthma severity, worse asthma related quality of life, and increased risk of asthma hospitalizations [34]. Cigarette smoking may also reduce the responsiveness to inhaled corticosteroids, the cornerstone of controller therapy for asthma [35]. Cigarette smoke can cause divergent inflammatory responses depending on host-factors. Although racial and ethnic differences in susceptibility to tobacco smoke is controversial, African Americans have been shown in several studies to have increased susceptibility to cigarette smoke with worsened lung function [36] and more rapidly progressing lung disease [37] compared to Caucasians.

Environmental tobacco smoke increases risk for new onset asthma, especially in those with a genetic predisposition [38]. Maternal environmental tobacco smoke exposure during pregnancy is associated with childhood asthma, even if the mother does not smoke actively during pregnancy [39]. When exposed in childhood, environmental tobacco smoke is associated with increased asthma symptoms, missed school days, and worsened lung function [40]. Environmental tobacco smoke is further known to increase asthma exacerbations and hospitalizations in both children and adults [41, 42].

1.8. Outdoor air pollution disparities

In numerous studies around the world, lower socioeconomic individuals live in areas with increased air pollution [43–45]. Lower socioeconomic individuals are more susceptible to poor health effects from air pollution; high socioeconomic individuals have access to more resources to protect themselves from exposure to air pollution such as private transportation (versus relying on public transit), indoor versus outdoor work environments, access to climate control, including filtration for indoor environments [45]. In addition, there are racial disparities to outdoor air pollution exposure: even after controlling for urban area size and socioeconomic status, racial minorities are more exposed to outdoor air pollution than whites [46].

Air pollutants, including particulate matter, gases (ozone, nitrogen dioxide and sulfur dioxide) and mixed traffic air pollution cause oxidative injury to airways that leads to inflammation and remodeling which can lead to incident asthma. Air pollution may also increase the risk of sensitization and subsequent inflammatory responses to inhaled outdoor allergens [47]. Asthma is widely accepted to be aggravated by air pollution [48] and more recent evidence suggests air pollution may also contribute to new onset asthma in children [49]. In a study of 10 European cities, 14% of the cases of incident asthma and 15% of all asthma exacerbations were attributed to air pollution near roadways [50].

Given the disparate exposure and susceptibility to outdoor air pollution within the poor and racial minorities, and given the known impact of this exposure on incident asthma and asthma morbidity, air pollution is an important factor to consider in the disadvantaged asthma patient.

1.9. Psychosocial stress: increased in the disadvantaged patient

In the US, racial minorities and the SES disadvantaged experience higher amounts of psychosocial stress [51]. Poor neighborhoods have less shops, banks, health care services and transportation. Residents in these communities must then spend expend a greater amount of time and effort to address basic tasks of living [52]. Lower SES communities have higher community violence and crime rates [53], and greater crowding and exposure to noise [54]. In disadvantaged neighborhoods, smaller social networks [54], and decreased "social capital" (which describes a community's investment in public goods and community services), leads to increased community stress, such as violence [55], and decreased community resilience to stress. Low SES neighborhoods are also less likely to foster facilities for stress outlets such as regular exercise, which may lead to health compromising efforts to cope with stress such as smoking and substance abuse [52].

Although psychosocial stress is commonly associated with disorders that cause significant respiratory distress, such as vocal cord dysfunction [56], stress can also affect individual biology, disease progression and management of asthma [57]. Stress has been linked to increased asthma expression [58]. An acute stress may increase the risk of asthma exacerbations through an enhanced Th2 immune response [59]. Chronic stress potentiates airway reactivity and inflammatory response to asthma triggers, such as allergens and infections [58, 60]. Increased inflammatory cytokines (IL4, IL5, IFN-Gamma) and increased asthma symptoms have been linked to acute stressful events in children who also have chronic stress [61]. Chronic stress increases susceptibility to environmental pollutants on incident asthma [62, 63]. Stress reduces expression of the B2-adrenergic receptor, and in turn reduces response to bronchodilators, a cornerstone of asthma management [64].

In some studies, stress has been an even stronger risk factor than environmental exposures for asthma morbidity [65]. Multiple sources of stress, commonplace in the disadvantaged asthma patient, have been associated with increased asthma morbidity.

Although housing stress can lead to increased environmental exposures, an often-overlooked health effect of living in substandard housing is the deprivation, disadvantage, and emotional toll experienced by asthmatics and their households [66].

Housing stressors, including housing insecurity, inability to pay rent, living without heat or electricity, or trouble with a landlord has been shown to worsen asthma morbidity [67, 68]. Stress related to immigration and acculturation factors has also shown to worsen asthma morbidity and increase emergency room utilization for asthma [69]. Intimate partner violence has been shown to increase asthma incidence in affected families [70]. Individuals who experience higher severity of food insecurity develop worse asthma symptoms [71]. Stress related to perceived discrimination has also been shown to affect asthma morbidity in racial and ethnic minorities [72].

1.10. Suboptimal adherence and medication use

Inhaled corticosteroids improve long-term outcomes in asthma patients, and current guidelines recommend inhaled corticosteroids as the backbone of inhaled regimens for those with persistent asthma [73]. Despite this recommendation, in a nationally representative population study in the US, less than 1/3 of those who meet guideline based recommendations for treatment with an inhaled steroid are using them [74]. This unfortunate reality of practice is further magnified in disadvantaged asthma patients. In a study of 1485 children, black and Hispanic children with persistent asthma had significantly decreased odds of using inhaled corticosteroids compared to white children. These undertreated minority children had more than twice the odds of being hospitalized for asthma in the past year compared to white children [75]. In another study of 190 African American or Hispanic adults recently hospitalized with asthma and the majority of which living in poverty, less than half were utilizing inhaled corticosteroids [76].

2. A multidisciplinary approach to personalize asthma therapy within the disadvantaged asthma phenotype

Phenotypic categorization of asthma patients is essential to individualize and optimize asthma therapy. Patients with a disadvantaged asthma phenotype are no exception. The social and

environmental factors described above are essential to identify in order to individualize a treatment strategy that addresses the relevant social and environmental factors (**Table 1**).

With this in mind, how do we first identify these important factors in our disadvantaged asthma patients? Although there is an increasing trend in understanding social determinants of health in medical education [77], most medical providers are not trained or provided with sufficient resources to identify and address the social and environmental challenges faced by the disadvantaged asthma patient. Previous studies have suggested that many providers recognize the importance of social and environmental factors, but do not routinely screen for or identify them in their practice [78]. Time constraints and the perception that most social and environmental needs cannot be remedied are often cited by clinicians as reasons for not diagnosing social and environmental needs in their patients [79]. However, given the importance that these factors play in asthma control in the disadvantaged asthma patient, identifying these factors should be considered a cornerstone of the medical history in these patients.

Emerging evidence suggests screening for social needs and connecting patients to existing community organizations or services can significantly improve health outcomes [80]. There are many publically available tools accessible to providers to help identify social needs in clinical practice [81], including some that easily integrate into electronic health record systems [82]. These screening tools will help providers to identify patients with exposures in substandard housing, as well the presence of other social determinants of health known to impact asthma outcomes in the disadvantaged such as inadequate health literacy, the presence of interpersonal and community violence, housing, energy and food insecurity. Although work related asthma is not a focus of current social needs screening tools, a three-question survey tool has recently been endorsed by the American Thoracic Society and the National Institute of Occupational Safety and Health and should be considered in disadvantaged adults with new onset or newly worsening asthma [83].

A number of nonconventional interventions can be considered to address other factors discussed above that are known to exacerbate the burden and severity of asthma in patients with a disadvantaged asthma phenotype. A multidisciplinary team with unique expertise to personalize delivery of care and address the individual social, environmental, economic and medical care should be considered.

Management strategy summary for the disadvantaged asthma phenotype
Screen for modifiable social and environmental factors
Utilize a multidisciplinary approach to address identified social and environmental factors, including partnerships with social workers, legal aid and community resources
Ensure adherence to a guideline-based asthma medication regimen, including attention to access to care, cultural beliefs, inadequate health literacy, and disparities in prescribing patterns
Recognize work related asthma, assist patients with reducing workplace exposures and accessing benefits when unable to work due to asthma
Counsel and assist patients regarding smoking cessation

Table 1. Management summary.

First, many providers will recognize that social workers are often at the forefront of helping to ameliorate the social and environmental conditions that impact asthma. Social workers are indeed often able to connect patients to community, hospital or government resources to address the needs of disadvantaged patients. However, although social workers are vital in the care of many disadvantaged asthmatics, the complex factors described in this chapter will require active engagement by medical providers as well as collaboration with professionals outside of the traditional medical team.

As described above, ensuring adherence to a guideline-based asthma medication regimen, most often centered on an inhaled corticosteroid, is an additional critical component to treatment of the disadvantaged asthma patient. There are multiple explanations to the underuse of controller medications in disadvantaged asthma patients including limited access to care, cultural beliefs, inadequate health literacy, and disparities in prescribing patterns leading to suboptimal quality of care [75]. Despite these barriers, using a culturally sensitive approach through asthma education programs targeting disadvantaged asthma patients, multiple pediatric programs have successfully improved adherence to preventive therapies and improved asthma outcomes [84]. Identifying reasons for suboptimal adherence, such as fear of adverse effects, fear of addiction, cost, inconvenience or complexity of treatment regimens can lead to an individualized conversation, education and medication regimen changes that can improve adherence in the disadvantaged asthma patient [85].

In this context, ensuring access and affordability of prescribed asthma medication is essential. In the US, disadvantaged patients are challenged by the lack of currently available generic inhaled corticosteroids and bronchodilators. Although inhaled corticosteroids and bronchodilators have been the mainstay of asthma therapy for over five decades, most of these medications remain under active patents for specific device delivery mechanisms, as well as chemical formulations. For the uninsured patient, the cost of an inhaled corticosteroid and or any bronchodilators can be upwards of $4000 annually. Even for those with commercial insurance, the out of pocket deductible can approach $500 per year [86]. High cost of inhalers in general is due to at least two major historical events. First, when the Montreal Protocol entered into force in 1989 [87], chlorofluorocarbons (CFC) was phased out with fear that CFC in inhalers could contribute to destruction of the ozone layer. Even though the contribution from the CFC in inhaler was infinitesimal, the urgency based on an assumption that the ozone layer would repair itself within 50 years led to complete ban of CFC including CFC in inhalers. Subsequent development of hydrofluoroalkane (HFA) led to reformulated inhalers and disappearance of generic inhalers. Second, producing generic inhalers is a complex process unlike generic pills. Each inhaler carries multiple patents consisted of specific chemical formulation (including HFA) and the delivery system (protected under the FDA as an investigational device). Such challenge is highlighted by the recent difficulty in bringing out generic Advair to the U.S. by two pharmaceutical companies (Mylan and Hikma). Mylan and Hikma Pharmaceuticals were prepared to bring generic Advair to US marker in spring of 2017. However, the FDA extended complete response letters to both companies, in early 2017 which effectively put the possibility of generic Advair well into 2018. The details of why these companies failed to obtain FDA approval are still unclear.

Inadequate access and affordability of asthma treatments is not unique to the US. In a study of 24 countries, the median cost of an inhaled corticosteroid was 20% of average local monthly per

capita income [88]. Inhaled steroids are not even available to be purchased in some developing countries. One example is in India, where low-income patients with asthma do not have access to any inhaled corticosteroid through the public health care sector [89].

Second, collaboration with lawyers is an unconventional approach that holds promise to address multiple social and environmental factors that drive asthma morbidity within the disadvantaged asthma patient [90]. Although there is evidence to support home environmental interventions such as carpet removal, air cleaners, allergen impermeable covering for bedding and pest control to improve asthma outcomes [91, 92], in many instances, these interventions are insufficient in the disadvantaged asthma patient. For example, patients living with leaky pipes, mold, pests, inadequate heat, or wrongful evictions are more challenging environmental problems to address using conventional environmental interventions. Lawyers can advocate through legal recourse including tenant-landlord law, housing code enforcement, eviction and utility shutoff prevention programs to improve factors known to exacerbate asthma in the disadvantaged patient. Often funded in part by Legal Services Corporation (an independent nonprofit established by Congress in 1974 to provide support for civil legal aid to low-income Americans), there are over 133 independent non-profit legal aid programs, at least one in every state [24]. Despite this funding, there remains a substantial gap between low-income Americans' civil legal needs and available resources to address them [93]. Increasingly health systems are recognizing the importance of legal solutions to many social and environmental problems [94] and future research is needed to study the effectiveness of legal interventions and partnerships to improve health outcomes, such as in asthma.

Third, work-exacerbated asthma, as described above, is often unrecognized by patients, clinicians and providers and contributes to worse clinical and socioeconomic outcomes in the disadvantaged asthma patient [24, 95]. Clinicians must assume an active role to connect workplace exposures to asthma symptoms. Recognizing the challenges disadvantaged asthmatic workers face provides opportunities to help. Work related asthma can frequently be managed by reducing workplace exposures and/or providing work accommodations. If unable to work to due to work related asthma, clinicians can help the disadvantaged asthma patient access available benefits.

Fourth, given the known socioeconomic and racial differences in smoking and environmental smoke exposure and given the effects of smoke exposure on asthma outcomes, smoking cessation is an important goal in the disadvantaged asthma patient. Smoking cessation is associated with improvements in lung function and reduction in asthma symptoms [96]. However, Black and Hispanic smokers are less likely to make successful quit attempts than whites [97], which is in part, because black and Hispanics are less likely than white smokers to have been screened for tobacco use and advised to quit by health care professionals [98]. With this in mind, it is essential to ensure smoking cessation counseling and resources are integrated into the management of the disadvantaged asthma patient who smokes. Smoking cessation programs that target disadvantaged smokers and include referrals to community resources that address the socio-contextual mediators of tobacco use (including referrals to community resources to help with job counseling, educational opportunities and physical activity) is highly effective at improving smoking cessation rates compared to a more traditional approach [99].

3. Conclusions

Most patients with asthma can be managed with standardized, traditional therapies; however, 5–10% of patients suffer from disease that is difficult to control. Uncontrolled asthma disproportionally affects low income and racial minority patients. The disadvantaged asthma phenotype is defined by the presence of overlapping social, economic and environmental factors. These factors, such as environmental exposures in substandard housing or suboptimal adherence to controller therapy due to impaired health literacy are challenging to address in the clinic or inpatient setting. Personalized management of the disadvantaged asthma phenotype must target these interconnected factors through a multidisciplinary approach that includes longitudinal collaboration with community-based organizations, social workers and legal aid.

Conflict of interest

All authors have no conflicts of interest pertaining to the entirety of the above chapter.

Author details

Drew A. Harris*, Caitlin Welch, Morgan Soper and Yun Michael Shim

*Address all correspondence to: drew.harris@virginia.edu

Department of Medicine, Division of Pulmonary and Critical Care, Complex Airways Diseases Program, University of Virginia, Charlottesville, Virginia, USA

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Chapter 6

Phosphodiesterase 3 and 4 Inhibition: Facing a Bright Future in Asthma Control

Jan Beute, Vincent Manganiello and Alex KleinJan

Additional information is available at the end of the chapter

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Abstract

A recent status on asthmaticus multiple case report by Beute demonstrated the beneficial effects of phosphodiesterase III (PDE3) and phosphodiesterase IV (PDE4) inhibition. This chapter reviews the possible underlying mechanisms, beside the known effect, for the beneficial effects of a mixed PDE3/4 inhibitor in allergic airway inflammation. Structural cells of the lung and immune system express PDE3 and 4. PDE3 and 4 inhibition have a number of consequences related to physical function and cytokine production. The most direct effect of PDE3 inhibition being relaxation of smooth muscle cells results in bronchodilation. However, PDE3 inhibition appears to go further than a mere inhibitory activity in bronchial smooth muscle. It also affects structural cells, and more importantly, it creates an improved barrier function in endothelial cells. PDE3 and 4 inhibition therefore strengthens the immune barrier; but in addition, it modifies the cells of the immune system itself, as these also express PDE3 and 4 activity, thus changing their function. All aspects of asthma-related pathophysiology seem to be affected by PDE3 and 4 inhibition. Clinical use of a mixed PDE3/4 inhibitor in respiratory diseases is currently limited to a few studies, including life-threatening asthma in which mixed PDE3/4 inhibition has a beneficial effect.

Keywords: PDE3, PDE4, allergic airway inflammation

1. Introduction

Asthma is an obstructive airway disease characterized by inflamed airways, structural and physiological abnormalities in the airways, and shortness of breath [1]. Important primary airway cells are alveolar cells, endothelial cells, and smooth muscle cells; and secondary cells

are involved in regulation of innate and adoptive immunology. Conventional treatment with inhaled corticosteroids combined with beta-adrenergic agonists supports and induces smooth muscle relaxation to reopen the inflamed airways, relieves symptoms, supports inspirational and expirational flow, and reduces inflammation [2]. These treatment regimens were also used in the extreme severe cases of asthma like status asthmaticus and patients with bronchospasm, in some cases with only minimal effect. The treatment goal in these severe cases of acute asthma is the prompt relief of respiratory distress. The great benefit of a mixed PDE3/4 inhibitor, in these severe cases, is the induction of acute as well as long-lasting bronchodilator effects [3].

At the moment, there is no effective treatment for these severe asthmatic patients [4] and there are no clear, effective guidelines. Moreover, treatment of these patients is multidisciplinary, involving first aid physicians, intensive care physicians, anesthetists, and pulmonary physicians, requiring golden standards and treatment regimens per hospital for optimal results. There are still too many asthma deaths; numbers in US are up to nine cases per day and in the UK are up to over three cases per day. Presently, in the Netherlands, there are annually more than 60.

This review discusses the PDE3 gene family and PDE3 inhibition, traditionally used in acute, refractory heart failure. We discuss the benefits of combined PDE3 and 4 inhibition in status asthmaticus [3], and the possible mechanisms which may be responsible for these beneficial effects of PDE3 and 4 inhibition.

2. The PDE superfamily: important regulators of cyclic nucleotide signaling pathways and networks

Intracellular signaling via complicated regulatory networks plays a critical role during physiological cellular responses. cAMP and cGMP were the first molecules described as intracellular second messengers [5]. They regulate multiple intracellular targets, including protein kinase A and protein kinase G, guanine nucleotide exchange proteins activated by cAMP (Epacs), cyclic nucleotide-gated ion channels, and PDE activities [6]. Intracellular concentrations of cAMP and cGMP are regulated through their synthesis by adenylyl cyclases (ACs) and guanylyl cyclases and their degradation via cyclic nucleotide PDEs. Ten different ACs have been identified and classified into two groups [7]. The first group consists of transmembrane enzymes which are activated by different hormones, neurotransmitters, chemokines, and cytokines in the G-protein-coupled receptor cascade [8]. Another group of cytosolic ACs is regulated by bicarbonate and calcium ions [8]. Whereas, cytosolic ACs are all encoded by one gene, transmembrane ACs represent a group encoded by nine different genes [9].

The large PDE superfamily is comprised of 11 PDE gene families (PDE1–PDE11). They specifically hydrolyze cyclic nucleotides, and can be classified according to their primary structures, tissue expression, biochemical properties, regulation, and their sensitivity to different pharmacological agents [10]. By catalyzing the hydrolysis of cAMP and cGMP, PDEs regulate the intracellular concentrations of these critical second messengers, and consequently, their downstream signaling pathways and networks. PDEs also function as important regulators in the compartmentation of cyclic nucleotide signaling pathways and networks. Individual PDEs are targeted/recruited to specific intracellular locations, where they are incorporated

into specific multiprotein regulatory complexes ("signalosomes") through protein-protein interactions. By virtue of their localization to specific compartments, PDEs can thus regulate specific cyclic nucleotide signaling pathways [11].

3. PDE3 and PDE4

PDE3 is expressed in pulmonary structural cells and cells of the immune system. Lung structural cells, including smooth muscle cells, epithelial cells, and endothelial cells, express PDE3. PDE3A and B are encoded by two highly related and similarly organized genes on human chromosomes, 12p12 and 11p15 [12–14]. Both PDE3A and PDE3B hydrolyze cAMP and cGMP, with 4–10 times higher affinity (Vmax) for cAMP [15]. Biochemical and histochemical studies of the localization of PDE3 suggested that PDE3 was associated with the sarcoplasmic reticulum, Golgi endosome, and nuclear envelope in cardiac tissue [16]. PDE3 plays a major role in cardiac contraction by modulating cAMP-dependent phosphorylation of voltage-gated Ca^{2+} channels and Ca^{2+} entry [17]. In addition, recent studies with PDE3A and PDE3B KO mice indicate that PDE3A, not PDE3B, regulates basal contractility in mouse heart [18].

Kass et al. described one mechanism, whereby PDE3 might be functionally modulated by cGMP occupying the PDE3 catalytic site [19]. PDE3 binds both cAMP and cGMP at its catalytic site with high affinity, and endogenous cGMP, generated by NO-induced activation of guanyl cyclase, can function as a competitive inhibitor of hydrolysis of cAMP by PDE3 [20]. NO-induced cGMP/cAMP cross-talk, mediated via cGMP inhibition of cAMP hydrolysis by PDE3 which leads to increased levels of cAMP, is thought to mediate some of the effects of NO in inflammatory and lung structural cells. NO modulates pulmonary vascular tone, causing non-adrenergic-, non-cholinergic-mediated bronchodilation [21]. Overexpression of nitric oxide synthase in both endothelial and airway epithelial cells resulted in diminished airway inflammation [22]. Under normal conditions of NO/cGMP signaling, PDE4, with a high Km for cAMP, is thought to degrade cAMP because PDE3 with a lower Km for cAMP is inhibited by endogenous cGMP and thus can increase cAMP [23]. PDE3-induced vasorelaxation is potentiated when NO/cGMP is suppressed as PDE3 inhibition increases both cAMP and cGMP, in which cGMP inhibits cAMP degradation. PDE4 inhibition only increases cAMP and thus is unaffected by NO/cGMP suppression [23]. PDE3 seems to be more responsible for cAMP degradation at low intracellular cAMP concentrations, whereas PDE4 is more important for control of cAMP at higher concentrations [24]. This suggests a beneficial effect of NO in allergic airway inflammation and urges caution in the use of NOS inhibitors [22]. Since the first PDE3 inhibition papers in the 1990s, 11 PDE families have been identified, and presently at least four isoforms of PDE4 are known [25]. Also, the idea of signalosomes has been postulated and partly verified [26].

4. Modulation of structural cells and immune cells by PDE3 and 4 inhibition

Several structural cells express PDE3. Inhibition of PDEs has a number of consequences in the pathophysiology of asthma.

4.1. Smooth muscle cells and cardiomyocytes

Cardiac muscle tissue and smooth muscles are not under conscious control. The role of PDE3 in cardiac muscle and in vascular and bronchial smooth muscle slightly differs due to regulation by different modulators and inhibitors [19]. Vascular SMC and airway SMC are widely comparable [27]. Reducing cAMP by PDE3 modulates contraction; PDE3 inhibition (PDE3i) leads to relaxation of vascular and airway SMC which results in vasodilation and bronchodilation due to the elevated levels of cAMP. NO activates soluble- and membrane-bound guanylate cyclases, which synthesize cyclic guanylate monophosphate (cGMP), which subsequently can serve as a competitive inhibitor of PDE3 as well as activator of cGMP protein kinases [16]. The downstream effects of NO are limited, in part, by phosphodiesterase (PDE)-induced degradation of cGMP [28].

The primary mechanism behind the PDE3 regulation of myocardial physiology relates to its control of cAMP levels; inhibition of myocardial PDE3, especially PDE3A, leads to decreased cAMP breakdown, resulting in increased cAMP which mediates positive inotropic effects and increases in myocardial contractility [29]. Although PDE3 inhibitors increase myocardial contractility and vasodilation in heart failure patients [29], prolonged use of the PDE3 inhibitor milrinone in these patients increased mortality was observed, most likely due to arrhythmias and cardiac arrest [30]. Presently, milrinone has an approval for short term treatment of untreatable exacerbations of heart failure and as a chemical "bridge to transplant" [31]. The work of Chen Yan and her colleagues suggests that the untoward effects of chronic administration of relatively high dosis of milrinone may possibly be related to long term effects of cAMP on pathological remodeling and progression of heart failure [32], via upregulation of inducible cAMP early repressor (ICER) and subsequent increases in cardiomyocyte apoptosis [33]. According to this hypothesis, PDE3 inhibitors increase cAMP, leading to increased expression of ICER, which blocks transcription of PDE3. This cascade of events induced a pathological "feedback loop," with downregulation or inhibition of PDE3 leading to increased cAMP/PKA signaling, upregulation of ICER, continued downregulation of PDE3, and enhanced apoptosis in cardiaomyocytes [33].

In smooth muscle cells, increased cGMP levels induce vasorelaxation. Due to effects of PDEs on hydrolysis of cGMP, PDE inhibitors play a major role in the fine-tuned regulation of this function. In addition to PDEs, NO plays an important role in vasorelaxation, perhaps, in part, by its activation of cytosolic guanylate cyclases, leading to increased production of cGMP, and subsequent inhibition of PDE3. The PDE3 inhibitor, cilostazol (Pletal), is widely used to treat intermittent claudication (IC), a lower-extremity peripheral arterial disease characterized by exercise-/ischemia-induced leg pain. It is thought that cilostazol increases walking distance and alleviates IC symptoms by cAMP-mediated vasodilation and inhibition of both platelet activation and vascular wall inflammation [34].

Asthma can present itself with varying levels of severity, and a particular subgroup of patients, labeled as "severe asthmatics" is characterized by the persistence of symptoms despite therapy with corticosteroids [2, 35]. Examination of bronchial airways from patients with severe asthma shows a greater amount of ASM (Airway Smooth Muscle) cell mass and of subepithelial fibrosis compared to non-severe asthmatics [36, 37]. In ex-vivo studies, ASM cells from severe asthmatics demonstrated increased cell growth and proliferation [38] and an increase in proliferating cell nuclear antigen, a marker of proliferation [39]. Cultured ASM cells from mild-to-moderate

asthmatics also proliferated faster than ASM cells from normal subjects [40]. Bhavsar et al. have previously demonstrated corticosteroid insensitivity in blood monocytes and alveolar macrophages from patients with severe asthma compared to those with non-severe asthma [41, 42]. Another feature of steroid insensitivity could be the ongoing ASM cell growth because the enhanced proliferation of ASM cells from patients with mild asthma is resistant to dexamethasone [43]. Given this perspective, it is of interest that studies with VSMC from PDE3A and PDE3B KO mice indicated that the absence of PDE3A, not PDE3B, diminished VSMC proliferation and indicated a G0 G1 cell cycle arrest [44]. PDE3 inhibition might reduce ASM proliferation in asthmatics.

4.2. Endothelial cells

Endothelial cells play an important role in the pathophysiology of asthma. Due to the expression of adhesion molecules, they enable cells to extravasate from the bloodstream into the inflamed tissue. Endothelial cells also possess a barrier function to prevent leakage of blood fluid in the tissue. Endothelial cells express PDE3 and 4, and inhibition of PDE3 and 4 of endothelial cells inhibited eosinophil and neutrophil adherence to monolayers of endothelial cells [45, 46]. PDE3 and 4 synergistically enhance the inhibition of VCAM1 expression and eosinophil adhesion to activated-human lung microvascular endothelial cells [45]. Inhibition of PDE3 leads to increases in cAMP which improves endothelial barrier functions and supports cell-cell junctions [47]. BW245c, a DP receptor antagonist, increases cAMP, and enhanced endothelial barrier function in a cAMP-dependent matter via the DP receptor, a G protein coupled receptor [48, 49]. Hyperpermeability of pulmonary endothelial monolayers, evoked by thrombin or *Escherichia coli* hemolysin, can be blocked by the simultaneous activation of adenylyl cyclase and inhibition of PDEs, especially PDE3 and PDE4 [50]. Sphingosine-1-phosphate (S1P1) induces endothelial cytoskeletal rearrangement and barrier enhancement by S1P1 receptor, PI3 kinase, Tiam1/Rac1, and alpha-actinin dependent mechanisms as well [51]. In vivo studies with asthma models indicate that compounds such as BW245c, sphingosine 1-phosphate receptor agonist (FTY720), and prostacyclin-2 analog (iloprost) impair Dendritic Cell (DC) migration [52–54]. This can be explained by a direct effect of these compounds on improving endothelial cell barrier function via elevated levels of cAMP [48, 55], which might affect DC migration from tissue to the draining lymph nodes.

PDE inhibition, a therapeutic approach to increase cAMP levels, was beneficial in treating capillary leakage and edema in a rat model of systemic inflammation induced by LPS [56]. Moreover, PDE3 inhibition was compared to dobutamine treatment (β-adrenoreceptor compounds); the former showed inotropic, lusitropic, and vasodilating properties which were not seen in patients treated with dobutamine [57, 58]. In bypass surgery patients, reduced inflammatory responses were observed during PDE3 inhibition compared to placebo treatment [59]. Furthermore, reduced TNF-α-levels, a cytokine which is increased in sepsis, were observed during PDE3 inhibition by enoximone compared to dobutamine-treated septic patients [58].

Hydrogen peroxide (H_2O_2), derived from neutrophils and other cells, supposedly is important in the development of vascular injury and thus of pulmonary edema. In a porcine pulmonary artery endothelial cell monolayer model, H2O2 increased hydraulic conductivity while selectivity was decreased. It is known that certain inhibitors of PDE isoenzymes 2, 3, and 4 could block H_2O_2-induced endothelial permeability [60]. The data suggest that adenylate cyclase activation/PDE inhibition is a powerful approach to block H_2O_2-induced increase in

endothelial permeability. This concept appears especially valuable when endothelial PDE isoenzyme patterns and PDE inhibitor profiles are matched optimally [61].

4.3. Epithelial cells, pneumocyte type I and type II

Human epithelial cells express PDE3 [62]. NO and cAMP both modulate membrane water permeability via aquaporin5 expression in pneumocyte type I [63, 64]. Experimental lung edema can be attenuated by selective PDE3 and PDE4 inhibitors [50, 65–67]. In experimental pulmonary edema, PDE3 inhibition reduces the numbers of inflammatory cells in BAL [66]. In alveolar epithelial cells, LPS-induced biosynthesis of proinflammatory cytokines is regulated by cAMP and tightly controlled by PDEs, and can be reduced by PDE inhibitors [68].

Inhibition of PDE3 and elevation of cAMP improve epithelial and endothelial barrier function and reduce SMC proliferation, which are interesting therapeutic targets in the future for asthma.

5. Immune cells

Mechanisms for regulation of PDE3 activity in immune cells, including dendritic cells, monocytes, B-cells, NK cells γδT cells, αβT-cells, T-cells, macrophages, eosinophils, and neutrophils, all of which express PDE3 isoforms are largely unknown (immgen database http://www.immgen.org/databrowser/index.html). Theophylline is a nonspecific PDE inhibitor [69]. In asthmatic patients, the inflamed airway mucosa, characterized by the presence of eosinophils, IgE positive mast cells, T-cells and dendritic cells, exhibits dysregulated barrier immunity [70]. These various inflammatory cells each have their own position in the asthma cascade. PDE3 and PDE4 are the major isoenzymes regulating IgE-stimulated mediator release from rat peritoneal mast cells [71]. Alveolar macrophage activation can be inhibited by PDE3/PDE4 inhibitors [72]. DC cultures were treated with a PDE4 inhibitor and with combined inhibition of PDE3 and 4; the latter resulted in a two times stronger reduction in LPS-induced TNFα release in DC cultures [73]. *In vitro* inhibition of PDE4 in DCs resulted in reduced development of Th1 cells as measured in reduced capacity to produce IL-12p70 and TNFα upon LPS or CD40L stimulation [74]. Peripheral blood monocytes from atopic dermatitis patients and healthy controls show inhibition of LPS-induced TNFα release during treatment with PDE4 inhibitors [75].

Inhibition of PDE3 and PDE4 prevents immunogen-stimulated IL-2 release from CD4 and CD8 human T-cells. Human T-cells and B-cell express PDE3 [73, 76–78]. Knock down strategies or inhibitors of PDE4B or D inhibit IL-4, IL-5, and IFNγ expression or production [79–81]. Peripheral blood mononuclear cells from atopic dermatitis patients and healthy controls show inhibition of PMA-induced proliferation due to the treatment with PDE4 inhibitors. cAMP was found to inhibit T-cell proliferation and differentiation which was linked to IL-2 [82, 83]. IL-2 activation of CD25+ T cells (Treg cells) led to a drastic upregulation in AC activity and to cAMP accumulation; an opposite significant decrease in AC activity was seen in CD25− T cells [83]. The PDE activity remained unchanged in both cell subpopulations, suggesting that the mechanism of cAMP accumulation in stimulated Treg involves AC7 activation [83].

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Cyclic AMP is a pleiotropic regulator of cell growth and function. In T-cells, cAMP suppresses TCR-triggered proliferation and cytokine production. cAMP is also a selective modulator of the actions of the proinflammatory transcription factor NF-κB. NF-κB plays a crucial role in switching on the gene expression of inflammatory and immune mediators and is therefore an important target for therapy [84]. cAMP is an important negative regulator of T cell activation, and increased levels of cAMP are associated with T cell hyporesponsiveness *in vitro* [85]. Stimulation of mouse CD4 T-cells by immature allogeneic DC combined with a PDE3 inhibitor resulted in functional Foxp3+ T-cells that delayed allograft rejection [86]. Moreover, PDE3 inhibition results in functional human Foxp3+ CD4+ T-cells which are driven by allogeneic APCs. The mechanism for these responses seems to be related to demethylation of FoxP3 gene [86]

Treatment with S-Petasin, an inhibitor of PDE3 and 4, reduced eosinophilic airway inflammation in an OVA model for asthma [87]. Although eosinophils do not express PDE3, reduced inflammation might be an indirect consequence of elevated levels of cAMP in endothelial cells that enhance endothelial barrier function and lowered the expression of adhesion molecules [45, 47]. PDE3 inhibitors sustained increased levels of cAMP in mast cells which are inhibitory to both basophils and human lung mast cells function [88]. Rat peritoneal mast cells showed reduced IgE-stimulated mediator release when treated with PDE3 inhibitors [71]. The conductive players in asthma, including T-cells and DC, and the central effector cells in asthma, including eosinophils, mast cells, basophils and neutrophils, can be targeted directly or indirectly with PDE3 inhibitors.

Recently, more and more interest is seen for the "old" theophylline which is a broad PDE inhibitor [69]. Theophylline [69] is a drug which targets PDE4 and, at high doses, also PDE3. However, it is a relatively weak bronchodilator at therapeutic concentrations. In patients, it is beneficial; and addition of theophylline can improve asthma control to a greater extent than beta2-agonist in patients with severe asthma [89]. Furthermore, in asthma patients poorly controlled by steroids, low dose theophylline added to inhaled corticosteroids improves asthma control [69]. The proposed mechanisms of action of theophylline include nonselective inhibition of PDE, antagonism of Adenosine receptors, inhibition of nuclear translocation of NF-κB, improved histone diacetylase 2, improved IL-10 secretion, induction of apoptosis of inflammatory cells (neutrophils and eosinophils) [90, 91], and inhibition of T-cell proliferation [85]. These features are of significant importance for severe asthma with poor steroid control, in which neutrophils are found and these patients were difficult to treat [4]. Theophylline exerted proapoptotic effects on monocyte-derived dendritic cells (DCs) and impaired DCs differentiation [90, 91].

6. PDE3 and 4 inhibition in the context of asthma

There is little literature available regarding enoximone in the context of airway disease. Bethke et al. showed that enoximone has inhibitory capacity on PDE3 and PDE4 [92]. Fujimura et al. researched cilostazol as a PDE3 inhibitor in asthma, showing its beneficial effect on bronchial hyper-responsiveness in elder asthmatics [93]. PDE4 inhibitors have been described in preclinical and clinical settings in the context of lung diseases like asthma and COPD [94, 95]. The PDE4 inhibitor roflumilast inhibits TGFβ-induced connective tissue growth factor (CTGF), collagen I and fibronectin in airway smooth muscle (ASM) cells of bronchial tissue rings [96].

Roflumilast is approved as part of the treatment regimen for Chronic Obstructive Pulmonary Disease (COPD) [97]. PDE3 inhibitors, including cilastozol, milrinone, and mixed PDE3/4 inhibitor enoximone, have mainly been used in the context of heart failure. Literature provides several cases with adverse effect and fatal outcome in the use of high dose PDE inhibitors for the chronic treatment of severe heart failure. A reason for this unfavorable outcome might have been that enoximone in heart failure was given in exceedingly high doses up to 2400 mg daily (31 mg/kg/dd) [98–100]; doses which were found to be extremely likely to cause severe side effects and a high mortality rate: after 6 months of treatment, at least half of the patients had died. Thus, the early research in pulmonary use has been abandoned and, since the late 90s, the sparse research into use of PDE3-inhibitors for pulmonary purposes has not led to the use of any of these drugs in the treatment of asthma. The first paper addressing actual clinical cases, in which enoximone treatment was given successfully in status asthmaticus and near fatal asthma was Beute [3], inspired by the resemblance between vascular and bronchial smooth muscle cell relaxation. In this paper, the doses used were considerably lower (1.15 mg/kg single dose) and the duration of administration was substantially shorter than in heart failure. Here, enoximone proved to be beneficial without side effects.

Enoximone is known as a PDE3 inhibitor that increases levels of cAMP as well as cGMP; however, in those cells where both compounds are present, cGMP will act as a competitive inhibitor on the breakdown of cAMP, thereby sustaining elevated levels of cAMP. cGMP can also be generated by nitric oxide (NO)-induced stimulation of guanylylcyclase (both abundantly present in smooth muscle cells), again impairing the breakdown of cAMP. The IC50 values of enoximone for PDE3 and PDE4 are 5.9 and 21.1 μM. The affinity of PDE3 for cAMP is 20 times higher than that of PDE4 [101].

These mechanisms probably allow for the favorable outcome of the relatively small doses of enoximone in Beute [3] and suggest an effect that exceeds its half-life.

Smooth muscle relaxation is more pronounced after administration of selective PDE3 inhibitors compared with PDE4 inhibitors. PDE3 inhibition leads to the enhancement of relaxation evoked by β2-receptor stimulation. Furthermore, simultaneous administration of siguazodan (PDE3 inhibitor) and rolipram (PDE4 inhibitor) enhances this relaxation, [102].

In **Figure 1**, both PDE3 and 4 are important in tailoring cyclic adenosine monophosphate signaling. PDE3/4 inhibitor increases intracellular cyclic adenosine monophosphate levels and has anti-inflammatory effects. Activation of a G-protein-coupled receptor (GPCR) activates adenylyl cyclase (AC) resulting in the induction of cAMP with the consequence of phosphokinase A (PKA) activation. Effect of PDE3/4 inhibition causes bronchodilation and improves endothelial and epithelial barrier function.

PDE4 is also present alongside the PDE3 isoenzyme in airway smooth muscle; the PDE3 isoenzyme is considered to predominate in airway smooth muscle, and inhibition of this enzyme leads to airway smooth muscle relaxation [103]. Moreover, PDE3 isoenzyme A is located in the cell membrane [25] and presumably easy to target, and could be involved in the rapid effects of therapy (minutes or earlier) seen during the intravenous emergency treatment in the studies of Beute [3].

Bringing to mind once again that all the cells and mechanisms mentioned in this chapter are regulated/influenced by either PDE3, PDE4, or both, and that all these cells and mechanisms

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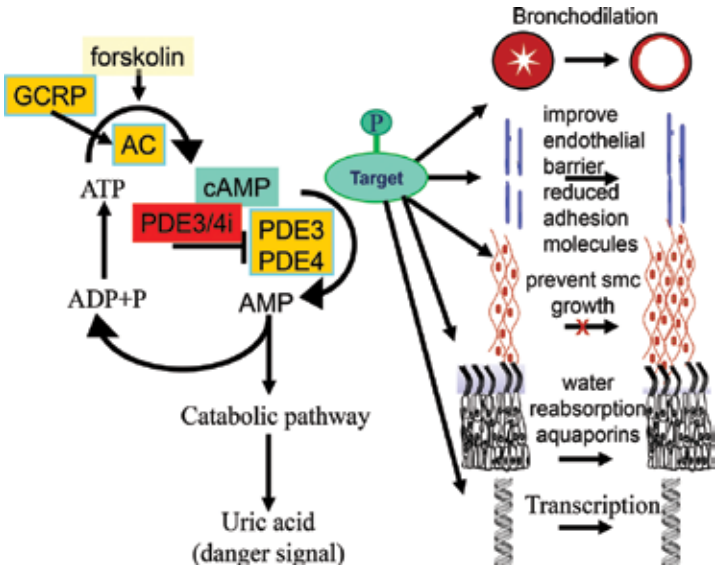

Figure 1. PDE3 and PDE4 inhibition improve harmful asthma-related processes.

are involved in the development, maintenance, or aggravation of asthma, there is a strong case for the assumption that enoximone may have a large impact on the acute treatment of severe asthma, on various separate levels. Additional safety studies will also be required.

As discussed above, further research in PDEs appears to be advisable in order to investigate their true potential.

Author details

Jan Beute[1], Vincent Manganiello†[2] and Alex KleinJan[1]*

*Address all correspondence to: a.kleinjan@erasmusmc.nl

1 Department of Pulmonary Medicine, Erasmus MC Rotterdam, Rotterdam, The Netherlands

2 Cardiovascular Pulmonary Branch, NHLBI, National Institutes of Health, Bethesda, Maryland

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Chapter 7

Subcellular Organelles in Immune Responses of Severe Asthma: The Roles of Mitochondria and Endoplasmic Reticulum

Yong Chul Lee and So Ri Kim

Additional information is available at the end of the chapter

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Abstract

Subcellular organelles including mitochondria and endoplasmic reticulum are now considered as one major target for many therapeutic approaches. In fact, recent evidence has uncovered the roles of mitochondria as a direct inflammatory and immune controller and contributor to the diseases by metabolic dysfunction and/or their abnormal dynamics. In addition, one of the important subcellular organelles, endoplasmic reticulum, also plays as an immune responder in several diseases including bronchial asthma. Recently, we have reported that the endoplasmic reticulum stress and mitochondrial reactive oxygen species (ROS) contribute to the pathogenesis of steroid-resistant severe bronchial asthma through the modulation of immune responses such as production of regulatory cytokines and NLRP3 inflammasome activation. These findings indicate that the subcellular organelles and their complex can be a promising target for the development of novel therapeutic strategies including medicines to cure severe asthma. This chapter is aimed to present the state-of-art information regarding the role of subcellular organelles in severe asthma.

Keywords: subcellular organelles, mitochondria, endoplasmic reticulum, inflammasome, severe asthma

1. Introduction

Subcellular organelle is a specialized subunit within a cell that has a specific function. Individual organelles are usually separately enclosed within their own lipid bilayers [1]. Specifically in eukaryotic cells, the organelles include nucleus, mitochondrion, endoplasmic reticulum (ER), Golgi apparatus, peroxisome, and lysosome which are found in the cytoplasm, a viscous liquid

found within the cell membrane that houses the organelles and is the location of most of the action happening in a cell. Each organelle plays the specific functions such as DNA storage, energy production, production of lipid and proteins, export of the proteins from the cells, protein modification, and destruction of lipid and protein, respectively.

Among them, ER is the largest organelle in the cell and is a major site of protein synthesis and transport, protein folding, lipid and steroid synthesis, carbohydrate metabolism, and calcium storage [2–6]. One of the most prominent functions of the ER is protein synthesis. When ER is overloaded by increased demand in protein folding, cells initiate an adaptive response called unfolded protein response (UPR). In addition, the ER's secretory pathway of its products and the ER-associated degradation (ERAD) pathway try to keep the homeostasis with full activity [7, 8]. ER stress can be developed, if ER fails to overcome the overloads and UPR are not able to make the ER adapt to the stressful conditions, despite all ER's efforts and adaptive responses. Recent considerable studies have demonstrated that ER stress is associated with the pathogenesis of several diseases such as neurodegenerative disorders, metabolic disorders, cardiovascular diseases, malignancies, and respiratory disorders [9–12]. More specifically, in severe asthma or steroid-resistant asthma, the role of ER stress has been highlighted in terms of regulation and interaction of various signaling pathways linked to steroid resistance [13]. In addition, nowadays, changes of ER shapes and structure responded to ER stress are emerging as one of pathogenic mechanisms regarding several disorders [14].

Mitochondria are energy-producing organelles which are dynamic and possess mitochondrial own DNA distinct from nuclear genome [15]. Basically, they are in charge of the synthesis and catabolism of metabolites, generation and detoxification of reactive oxygen species (ROS), apoptosis, regulation of calcium, and generation of adenosine triphosphate (ATP) by oxidative phosphorylation [16]. Recently, a novel role for mitochondria has been revealed in various disorders such as infectious diseases, neurodegenerative diseases, cerebrovascular diseases, and metabolic diseases, especially in the association of innate immune and inflammatory responses [16–19]. In addition, our recent study has revealed that exceed generation of mitochondria ROS and alteration of mitochondrial DNA induced steroid-resistant neutrophilic asthmatic features through the activation of NLRP3 inflammasome in mice [20]. More interestingly, mitochondria are highly motile organelles. In fact, we know that mitochondria actively travel along the microtubule network in neurons and accumulate at sites of high-energy demands [21]. These mitochondrial dynamics and morphological changes are through constitutive cycles of fusion and fission [22]. Nowadays, impaired processes of mitochondrial dynamics have been accepted as a pathogenic contributor to various disorders, including lung diseases [23, 24].

The last decades have witnessed an explosion in the elucidation of the causative mechanisms implicated in bronchial asthma, especially severe or steroid-resistant asthma; however, the treatment of asthmatic patients is still challenging. One of the reasons can be that many newly developed therapeutic tools are single-targeted and linked to the shortage of broad clinical effect, although they might be effective in asthmatic patients with specific phenotypes. On the other hand, drugs with more widespread effects (e.g., kinase inhibitors) might be more effective pharmacologically, whereas the potential risk of side effects might increase [25].

Therefore, novel treatments should be considered to target the aspects of the multiple underlying allergic/immune/inflammatory processes and minimize the adverse effects on other systems. In terms of this point, targeting subcellular organelles, especially ER and mitochondria, has a strong competitive power for the development of future medications of asthma, especially steroid-resistant asthma, since restoration of their abnormal function to normal physiologic status of each subcellular organelle is going without serious adverse effects unlikely to the existing therapeutic approach of blocking or eliminating the pathogenic targets.

2. Severe asthma and its heterogeneity

For many years, the term severe asthma has been used interchangeably with other similar terms, and considerable effort has been concentrated to be uniform in the term and concept. Several academic societies and research groups have suggested the definition of severe asthma such as European Respiratory Society (ERS), American Thoracic Society (ATS), World Health Organization (WHO), and British Thoracic Society (BTS)/Scottish Intercollegiate Guideline Networks (SIGN) [26–30]. In various definitions of severe asthma with little differences, there is a common ground that severe asthma can be defined as a failure to achieve control with maximum doses of inhaled corticosteroid therapies [31]. Taken together, severe asthma contains the existing disease entities; steroid-insensitive asthma, steroid-resistant asthma, difficult asthma, and refractory asthma, and these subsets of asthmatics have been estimated up to 5–10% of all asthmatics.

Although there are still many different definitions for severe asthma available and difficulties in making an accurate definition for severe asthma, numerous data based on these definitions consistently demonstrate the heterogeneity of severe asthma in populations with asthma [32, 33]. In fact, in 2001, the National Heart, Lung, and Blood Institute initiated the Severe Asthma Research Program (SARP) to identify and characterize not only a large number of subjects with severe asthma but also to compare these subjects with those with mild to moderate asthma [34]. In the SARP adult clinical cluster analysis, five different groups of subjects with asthma were identified who differ in clinical and pathophysiologic parameters [33]. These five asthma phenotypes differ in lung function, age of asthma onset and duration, atopy, sex, symptom frequency, medication use, and health-care utilization. Clusters 1, 2, and 4 reflect the spectrum of allergic asthma from mild to severe airflow obstruction. The majority of these patients have early-onset disease, with history of atopy confirmed by skin prick testing and elevated total serum IgE. By contrast, Clusters 3 and 5 reflect the spectrum of adult-onset asthma characterized by older patients with less atopy, yet, high health-care utilization and poor quality of life [33]. The SARP clinical heterogeneity, even in severe asthma group, can provide a basis for the needs to investigate the different molecular and biological mechanisms and different therapeutic approaches for the patients with severe asthma. In addition, SARP cluster analysis revealed inflammatory heterogeneity through the evaluation of blood and sputum inflammatory cells. In addition, the data suggested that sputum eosinophils were increased in Cluster 4 subjects with severe allergic asthma, whereas both eosinophils and neutrophils were increased in subjects from Cluster 5 [33]. A sequential study has reported that

grouping of subjects based on their sputum inflammatory cell profile identified four groups of subjects with distinguishing clinical characteristics [35]. For instance, patients showing both eosinophil (≥2%) and neutrophil (≥40%) predominant pattern, called as mixed granulocytic pattern, had the most severe asthma with severe chronic airflow obstruction and increased symptoms with high health-care utilization. In addition, according to this paradigm, all five clinical clusters of SARP showed all four patterns of sputum inflammatory profiles without a dominant pattern in any one cluster [34]. The lack of association between the clinical clusters and sputum inflammatory cell patterns does not only make the heterogeneity of severe asthma more complex but also emphasize that future analyses must incorporate clinical, physiologic, and inflammatory measures into one analysis [36].

Very recently, an interesting study of cluster analysis data has been released using U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) severe asthma cohort [37]. In this study, three transcriptome-associated clusters (TACs) were defined: TAC1 characterized by immune receptors IL33R, CCR3, and TSLPR, TAC2 characterized by interferon-, tumor necrosis factor (TNF)-α, and inflammasome-associated genes, and TAC3 characterized by genes of metabolic pathways, ubiquitination, and mitochondrial function. Subjects with severe asthma were classified into these three clusters based on their sputum transcriptomics data. Each TAC group exhibits their own differential clinical features: one Th2-high eosinophilic phenotype TAC1 and two non-Th2 phenotypes TAC2 and TAC3, characterized by inflammasome-associated and metabolic/mitochondrial pathways, respectively. This analytic approach is unlikely to previous ones such as SARP which showed the lack of association between the clinical clusters and sputum inflammatory cell patterns. Considering that clustering using clinical features alone has not yielded information on the underlying biology as similar inflammatory cell profiles have been seen between these clinical clusters [34], this study is worthy to approach with the unconventional direction from inflammatory or biologic clustering to clinical phenotyping. This approach provides a fresh framework on which to phenotype asthma and a more precise targeting of specific treatments [38]. Specifically, the development of novel medications has been poorer, targeting non-Th2 or non-type-2 severe asthma than Th2 or Type-2 severe asthma. In terms of this issue, this novel-clustering analysis data are expected to be helpful for the development of the medicines targeting non-type 2 asthmatics. In fact, two non-Th2 phenotypes TAC2 and TAC3 are associated with inflammasome and mitochondrial pathway, respectively. In addition, while the majority of subjects in TAC2 group show neutrophilic predominant inflammatory pattern, the subjects in TAC3 group can be further divided into paucigranulocytic, eosinophilic, and neutrophilic pattern subgroups. Interestingly, the differential characteristic of eosinophilic TAC3 subjects from Th2-type TAC1 subjects is the elevated levels of inflammasome, suggesting that non-Th2 type asthma can also have eosinophilic-dominant inflammation partly through the activation of inflammasome.

Considering nowadays the concept of severe asthma and heterogeneity, the improvement of the detailed characterization of the patients is required to achieve appropriate therapeutic responses for severe asthma. It is expected that the correct determination of phenotype and molecular endotype leads to more effective precision medicine for severe asthma.

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3. ER stress in severe asthma

As introduced, ER is a specialized organelle that plays as an important regulator of protein homeostasis in cells of an organism. The ER is rich in chaperones and enzymes that help to fold the protein properly. ER chaperones and enzymes are fragile to various stresses; thus several stressful or pathologic conditions (e.g., disease situation) may lead to the impaired ER protein-folding capacity leading to the accumulation of misfolded and unfolded proteins in the ER lumen. This out-of-controlled state of ER is usually called as ER stress [13, 39, 40].

Three ER transmembrane sensors are inositol-requiring enzyme 1α (IRE1α), double-stranded RNA-dependent protein kinase (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6). The functions of the ER membranous proteins include monitoring protein homeostasis of ER lumen and activation of canonical UPR pathways to deliver the information on the ER status to cytoplasm [40, 41]. According to the classic model of the activation of UPR, in basal conditions, these three transmembrane proteins are bound by a chaperone, BiP/glucose-regulated protein 78 (GRP78) [42, 43]. The development of ER stress causes the separation of BiP from these UPR sensors bound. The activation of IRE1α and PERK is associated with the dimerization and auto-phosphorylation, while in case of ATF6, its translocation to the Golgi is required to get activated [7]. Activated forms of proteins mitigate ER stress through the reduction of protein synthesis, the enhancement of protein degradation, and the induction of production of ER chaperones. When the protective process fails to resolve ER stress, the cell is prepared for apoptosis which is also one of the biological protective mechanisms [44]. Recently, in addition to these canonical UPR, noncanonical aspects of UPR confer cells to interconnect protein homeostasis-related cellular apparatus to a wide array of cellular events including immunity and inflammation through various mechanisms, as substantially reviewed elsewhere [45, 46].

In addition, the complex roles of ER including protein synthesis and lipid synthesis, calcium regulation, and interactions with other organelles are reflected in an equally complex physical architecture. The ER is composed of a continuous membrane system that includes the nuclear envelope and the peripheral ER, defined by flat sheets and branching tubules [14]. While it is generally known how the basic shapes of ER sheets and tubules are determined, it is relatively unclear how changes in the shape or the ratio of sheets to tubules occur in response to specific cellular signals. In several conditions, increasing ER loads and ER stress such as mitosis, changes of ER structure, and shapes are noted. In fact, recent studies showed that splicing of XBP1 is activated during meiosis in both *Xenopus* and budding yeast [47, 48], suggesting that changes in ER structure during meiosis could be linked to the ER stress response. However, to date, it is remained unclear whether ER stress induces immediate restructuring of ER or not. In the same vein, it has not yet been determined whether the activation of ER stress-responsive-signaling pathways results in a modification of structural components of the ER [14].

Accumulating data have indicated that ER stress and UPR link to major inflammatory and stress-signaling networks including the nuclear factor kappa B (NF-κB) pathway and oxidative stress. Recent studies have unveiled the role of ER stress in the pathogenesis of various

pulmonary disorders, including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and acute lung injury [9, 49–52].

As for bronchial asthma including severe form, the role of ER stress has been reviewed elsewhere [13, 40, 52]. In particular, neutrophilic steroid-resistant severe asthma animal model, which is similar to human TAC2 group, exhibited the significant increases in ER stress markers, GRP78 and CCAAT/enhancer binding protein-homologous protein (CHOP), as well as UPR-related proteins in lung tissues and BAL cells [9]. The mice showed typical asthmatic manifestations including bronchial hyperresponsiveness and airway inflammation which were not attenuated by the treatment with oral dexamethasone. Intriguingly, an ER stress regulator, 4-phenylbutyric acid (4-PBA), effectively attenuated steroid refractory asthmatic features as well as increases in ER stress linked to NF-κB activation which induces various severe inflammatory/immune responses in the lung. In addition, 4-PBA dramatically reduced the increased expression of IL-17, while it further enhanced the increase in IL-10 levels, leading to the attenuation of steroid-resistant asthmatic features. In another recent study using the same animal model [20], the activation of NLRP3 inflammasome was measured. The results revealed that NLRP3 inflammasome was significantly activated in lung tissues and BAL cells from neutrophilic-dominant severe asthma murine model and that the severe asthmatic symptoms were dramatically attenuated by the blockade of IL-1β which is one of major effector cytokines by NLRP3 inflammasome activation. A more recent study using another neutrophilic-dominant steroid-resistant asthma animal model and human data also has revealed the significant role of NLRP3 inflammasome in the pathogenesis of neutrophilic-dominant severe asthma [53]. These findings suggest that the neutrophilic-dominant steroid-resistant or severe asthma animal models can represent the TAC2 group of human severe asthma characterized by IFN, TNF-α, and inflammasome-associated genes and that ER stress can be more associated with this clustered asthma. A recent study has also demonstrated that ER stress inducer, tunicamycin, aggravates ER stress in mouse bronchial epithelial cells and increased the expression of inflammation indicators such as IL-6, IL-8, and TNF-α in lung tissues of neutrophilic severe asthmatic mice [54]. The double-stranded RNA (dsRNA)-activated serine/threonine kinase R (PKR) is well characterized as an essential component of the innate antiviral response. In view of the relation with ER stress, PKR phosphorylates e-IF2α, one of the branches for UPR, and at the same time, ER stress activates PKR which stimulates various inflammatory-signaling pathways [55, 56]. With this background, a recent interesting study showed that poly (I:C)-induced exacerbation of neutrophilic severe asthmatic mice was closely associated with PKR phosphorylation as well as increased ER stress in lung tissues including bronchial epithelial cells [56].

In addition to neutrophilic severe asthmatic phenotype, eosinophil-dominant severe asthma with fungal sensitization also showed the significant elevation of ER stress in mice [57]. In this study, *Aspergillus fumigatus* extract-inhaled mice showed typical asthmatic manifestations including eosinophilic airway inflammation and airway hyperresponsiveness which were not responded to treatment with oral steroid, while all asthmatic features and increased ER stress were very well controlled by 4-PBA, suggesting that ER stress is linked to the pathogenesis of eosinophilic-dominant severe asthma as well as neutrophilic-dominant one. Meanwhile, this animal model appeared to represent the TAC3 human severe asthma group. As described

earlier, TAC3 is characterized by genes of metabolic pathways, ubiquitination, and mitochondrial function, and the subjects of TAC3 exhibit various inflammatory cell types including paucigranulocytic, eosinophilic, and neutrophilic pattern subgroups. Thus, this fungal extract-inhaled eosinophilic severe asthma murine model can be considered as an eosinophilic pattern TAC3, non-Th2 eosinophilic asthma. Actually, in this study, mitochondrial ROS was significantly increased in the lung from *A. fumigatus* extract-inhaled mice [57].

These observations suggest that ER stress plays a critical role in the pathogenesis of various phenotypes of severe asthma including neutrophilic, eosinophilic, and viral infection-related types, supporting that the ER stress-targeting strategy seems to be able to overcome the steroid resistance in severe asthma.

4. Mitochondria in severe asthma

Asthma is characterized by ongoing inflammation and accompanied by increased oxidative stress and subsequent lung injury. ROS production, which leads to oxidative stress, is one of critical features in chronic airway disorders [58]. Two major sources of ROS induced by external stimuli are mitochondria and the Nox family of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in vivo. Besides, the mitochondrial respiratory chain is considered to be an important part of ROS production within most cells [59]. In addition, the considerable interplay between mitochondria and ER in several respiratory disorders has been demonstrated [59, 60]. In fact, fungal extract-inhaled mice exhibiting features of eosinophilic severe asthma or representing eosinophilic TAC3 showed significant increases in the production of mitochondrial ROS in BAL cells [57]. *A. fumigatus* extract-stimulated tracheal epithelial cells from the mice also markedly more generated mitochondrial ROS compared to the control cells [57]. In addition, treatment with NecroX-5, a potent mitochondrial ROS inhibitor, effectively attenuated increases in mitochondrial ROS in BAL cells, reduced increases in GRP78 and CHOP in lung tissues from *A. fumigatus* extract-inhaled mice, and ameliorated pathophysiologic features of fungal extract-induced eosinophilic severe asthma. In addition to eosinophilic severe asthma, recent experimental data using ovalbumin (OVA) and lipopolysaccharide (LPS)-sensitized and OVA-challenged mice (OVA-LPS mice) representing TAC2 revealed that the increased generation of mitochondrial ROS and the alteration of mitochondrial DNA induced steroid-resistant neutrophilic asthmatic features through the activation of NLRP3 inflammasome in lung and that the restoration of mitochondrial ROS levels using mitochondrial-specific ROS scavenger dramatically attenuated steroid-resistant airway hyperresponsiveness and inflammation in mice [20]. These findings suggest that mitochondrial metabolic dysfunctions such as mitochondrial ROS generation and mitochondrial DNA damage are linked to other subcellular organelles (e.g., ER) and immunologic complex (e.g., inflammasome) in the pathogenesis of steroid-resistant asthma and that mitochondrial ROS plays a key role in the induction and maintenance of neutrophilic and eosinophilic steroid-resistant severe asthma. As supporting data, when N-acetylcysteine (NAC), which is a representative conventional antioxidant, was administered to both types of steroid-resistant severe asthma murine models, for example, eosinophilic and neutrophilic types, NAC did not affect

steroid-resistant asthmatic features, mitochondrial ROS generation, and NLRP3 inflammasome activation (unpublished data), suggesting the importance of the role of mitochondrial ROS generation in the pathogenesis of steroid-resistant severe asthma as well as one of causes for the previous failures in the clinical trials for asthma patients to evaluate the effects of various conventional antioxidants.

Like this, mitochondria perform many roles beyond energy production, including the generation of ROS, redox molecules, and metabolites; regulation of cell signaling and cell death; and biosynthetic metabolism [61–63]. Thanks to these observations, mitochondria have recently become a promising target for the treatment of various inflammatory disorders, including bronchial asthma. However, most studies regarding mitochondria as a pathogenic contributor have dealt with mitochondrial metabolic dysfunction or mitochondrial genetic abnormality. As introduced, mitochondria are not static, highly dynamic in cells, and change the morphology.

Mitochondrial morphology is controlled by large guanosine triphosphatases in the dynamin family [64]. Among them, mitofusins 1 and 2 (MFN-1 and MFN-2) and optic atrophy protein 1 (OPA-1) are essential mediators of mitochondrial fusion [65]. By contrast, fission requires dynamin-related protein 1 (DRP-1) to be recruited from the cytosol to the mitochondrial surface [66]. Mitochondrial fission is known to be prevalent in diseased cells, with subsequent elimination of damaged mitochondria via mitophagy [67]. By contrast, mitochondrial fusion inhibits apoptotic cell death [22]. In fact, several reports have demonstrated that increased mitochondrial fission and decreased fusion are observed in cells from various lung diseases such as lung cancer [68, 69]. Interestingly, our preliminary data have revealed that mitochondrial dynamics were out of control in *A. fumigatus* extract-inhaled mice, and the restoration of abnormal mitochondrial dynamics could attenuate the steroid-resistant airway inflammation and airway hyperresponsiveness (unpublished data), providing the novel concept that a therapeutic strategy targeting mitochondrial dynamics can overcome steroid resistance in severe asthma. However, we are only beginning to evaluate and understand the related mechanisms and the role of mitochondrial dynamics in the pathogenesis of severe asthma. More future researches and studies are needed to support the role of mitochondria in the pathogenesis of severe asthma. In addition, the identification of the specific phenotype and/or endotype related to mitochondrial metabolic and morphologic dysfunction is eagerly required for the patient-oriented treatment or the precision medicine of severe asthma.

5. Potential clinical biomarkers and therapies related to mitochondria and ER

Biomarkers may facilitate the diagnosis and classification of severe asthma, predict efficacy of specific therapies, and assess medication response. Based on the data, to date, there are some potential biomarkers related to ER, mitochondria, and inflammasome in severe asthma. More specifically, the biomarker candidates are considered as the biomarkers for the prediction of efficacy of the subcellular organelle targeting therapies and for assessment therapeutic responses.

In fact, ER stress markers, GRP78 and CHOP, have been measured in BAL fluid from asthmatic patients [9]. Very interestingly, the levels were increased in BAL fluid from asthmatics compared to the levels from the healthy persons. The asthmatics were composed of patients who had been diagnosed and treated for asthma for more than 3 months with inhaled corticosteroid or combined inhaled corticosteroid and beta-β_2-agonist. In addition, the patients exhibited uncontrolled asthmatic symptoms scored below 19 points by asthma control test (ACT) scoring system despite the standard treatment including inhaled corticosteroid. Although the protein expression levels of GRP78 and CHOP were not correlated with the lung function, the protein expression reflected the asthmatic-controlled status in humans supported by the data from animal experiments, in which steroid-responded asthmatic mice showed the decrease in the expression levels of GRP78 and CHOP in lung tissues by the treatment of steroid, while the steroid-resistant asthmatic mice were refractory to the treatment with steroid in terms of the protein levels. When an ER stress inhibitor, 4-PBA, was administered to the steroid-resistant asthmatic mice, the levels of GRP78 and CHOP were substantially reduced in lung tissues and BAL cells with the attenuation of asthma symptoms [9]. These findings suggest the potential of the use of GRP78 and CHOP as biomarkers, classifying the patients into steroid-responsive group and steroid-resistant group after the standard treatment including inhaled corticosteroid as well as predicting or monitoring the therapeutic responses of ER stress inhibitor as a medication for severe asthma.

Mitochondrial ROS can be another biomarker candidate. In asthma, there is an elevated airway expression of products of oxidative stress. Actually, exhaled breath condensate levels of oxidative stress-related biomarkers, such as hydrogen peroxide (H_2O_2), nitrite/nitrate, 8-isoprostane, and others vary with asthma exacerbations, disease severity, and medication use [70]. As mentioned earlier, mitochondrial ROS may be a more critical player in the pathogenesis of severe asthma compared to general or total cellular ROS generation. Nowadays, several tools including simple detection kits and staining indicators have been introduced for measuring the specific mitochondrial ROS levels which distinct from the total cellular ROS generation in vivo. Thus, in addition to cellular ROS, mitochondrial ROS in various biological samples such as exhaled breath condensate, sputum, and BAL fluid can be expected to be one of biomarkers of the next generation for the diagnosis of severe or steroid-resistant asthma. Moreover, the studies using recently developed mitochondrial ROS inhibitor, NecroX compounds, have reported the excellent efficacy of this chemical as a potent and specific mitochondria-targeted antioxidant in several disease models [71–75]. Even in human studies, a phase II clinical trial is currently being performed to evaluate the efficacy, safety, and pharmacokinetics of intravenous injection of NecroX-7 immediately before percutaneous coronary intervention in patients with myocardial infarction (ClinicalTrials.gov; NCT02770664). Therefore, it can be hypothesized to consider that NecroX compounds may be developed as a novel therapeutic agent to control or cure the steroid-resistant severe asthma in future.

Furthermore, mitochondrial ROS is closely associated with the assembly of inflammasome, specifically NLRP3 inflammasome, which is formed by various stimuli in the inflammatory state. NLRP3, one of the cytosolic pattern recognition receptors, plays as one of the components of the inflammasome and recognizes a variety of inflammatory stimuli, pathogen-associated molecular pattern molecules (PAMPs), and damage-associated molecular pattern molecules (DAMPs) in cells. Subsequently, the assembled and activated NLRP3 inflammasome controls the production of important pro-inflammatory cytokines such as IL-1β and IL-18 [76]. Two

common events that are required for these activators of the NLRP3 inflammasome are potassium efflux and ROS generation [77]. Recent interesting studies have revealed that steroid-resistant neutrophilic asthmatic manifestations were significantly controlled by the NLRP3 inflammasome activation, and the severe asthmatic symptoms were dramatically attenuated by the blockade of IL-1β or inflammasome inhibitor, MCC950 [20, 53]. Moreover, increased NLRP3 and IL-1β sputum gene expression were strongly associated with increasing asthma severity in humans, suggesting that the NLRP3 inflammasome is important in human disease as well [53]. In addition, the protein expression levels of NLRP3 and caspase-1 were more increased in BALF from uncontrolled asthmatics compared to healthy subjects [20]. Taken together, these data suggest the potential of NLRP3, IL-1β, or caspase-1 to use as diagnostic and therapeutic biomarkers in respiratory specimens and urge to perform the translational or clinical studies regarding this issue. In addition, until now, there are no interventional clinical data applying the agents targeting NLRP3 inflammasome such as MCC950 in steroid-refractory severe asthma; however, it can be a very promising target for the control of severe asthma.

Altogether, it is clear that there are huge needs for further researches and future translational and clinical studies to use the candidate markers and therapeutic agents related to subcellular organelles in clinical practice.

6. Conclusion and future directions

Severe asthma is characterized by uncontrolled symptoms and recurrent exacerbation with excessive chronic airway inflammation despite adequate and even maximum treatment with the current medications. Although multiple factors can cause poor responses and underlying pathogenic differences are being revealed explaining the various therapeutic responses including steroid insensitivity, effective therapeutic modalities for severe asthma still remain as a major unmet need [78]. To overcome these current obstacles, cluster analysis and research for the heterogeneity of severe asthma are actively ongoing. Recent unconventional approach to define the clusters of subjects with severe asthma using TACs seems to be more helpful for the development of precision medicine for severe asthma compared to conventional clinical feature-based clusters, although more future supporting researches are needed. In addition, the heterogeneity of severe asthma is going to be more complex as the cluster analytic tools are advanced.

Recently, accumulating findings suggest that the regulation of ER stress and the restoration of mitochondrial dysfunction are prospective molecular therapeutic approaches for various pulmonary disorders including bronchial asthma. More encouragingly, the inhibition of ER stress overcomes the failure of steroid in attenuating the severe asthmatic features of mice including non-Th2 neutrophilic type (similar to TAC2) as well as the eosinophilic type (similar to TAC3). Furthermore, as we described earlier, therapeutic approach to control ER stress is able to regulate multiple integrated signaling networks concomitantly known as the famous pathogenic mechanisms for steroid-resistant inflammatory responses. In addition, the link between ER stress and mitochondrial ROS generation is very interesting in severe asthma.

Interestingly, in non-Th2 neutrophilic severe asthma, NLRP3 inflammasome assembly is activated and consequently induces IL-1β production and release. In addition, mitochondrial

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ROS generation and the mitochondrial DNA damage are closely associated with NLRP3 inflammasome activation in this animal model of severe asthma. Meanwhile, in non-Th2 eosinophilic steroid-resistant asthma induced by fungal extract, mitochondrial dysfunction on their dynamics or morphology as well as ROS generation is observed, which resulted in steroid-resistant airway inflammation and hyperresponsiveness in mice. Therefore, the restoration and inhibition of mitochondrial dysfunction can be a novel promising target for the therapeutics of severe asthma. Considering the link among ER, mitochondria, and inflammasome, their interconnection can be suggested as a more powerful tool for the control of severe asthma (**Figure 1**).

Despite success in mice, to date, there is the shortage of information on molecular mechanisms, explaining these effects of the control for ER stress and mitochondria, and there are also no clinical trials that evaluate the therapeutic effects of the pharmacologic agents targeting subcellular organelles in humans. In addition, since the subcellular organelles play essential roles in the body, the adverse effects of the pharmacologic intervention targeting ER or mitochondria must be considered. However, as for the adverse effects, since this therapeutic approaching concept is aimed to restore the stressful or dysfunctional condition into the physiologic levels, not to block the function or to null, it seems to be superior to other new therapeutics pursuing the single specific target blockade.

In conclusion, the restoration of subcellular organelles in a disease state is a potentially exciting target for developing agents to achieve better management of severe asthma in which steroids and other current agents are less effective.

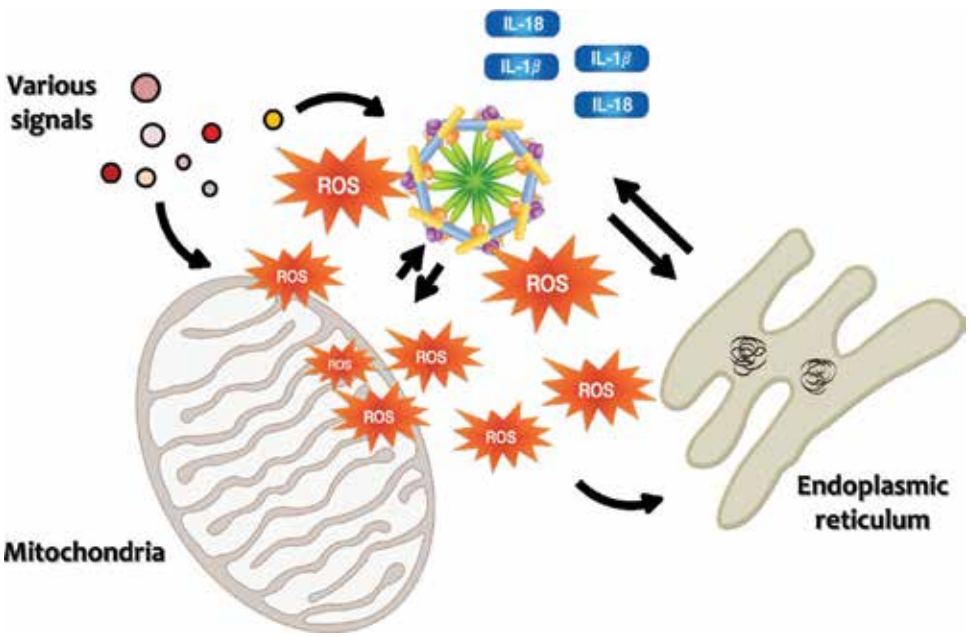

Figure 1. Schematic diagram of the possible interconnection among endoplasmic reticulum, mitochondria, and inflammasome in the pathogenesis of steroid-resistant asthma.

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Conflict of interest

The authors have declared that no conflict of financial interest exists.

Author details

Yong Chul Lee and So Ri Kim*

*Address all correspondence to: sori@jbnu.ac.kr

Division of Respiratory Medicine and Allergy, Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, South Korea

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Section 2

Biomarker and Phenotype Driven Asthma Management

Chapter 8

Severe Asthma: Updated Therapy Approach Based on Phenotype and Biomarker

Marcia Regina Piuvezam,
Laércia Karla Diega Paiva Ferreira,
Talissa Mozzini Monteiro,
Giciane Carvalho Vieira and
Claudio Roberto Bezerra-Santos

Additional information is available at the end of the chapter

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Abstract

Asthma is responsible for considerable global morbidity and health-care costs affecting over 300 million people worldwide. This illness is a heterogeneous condition characterized by chronic airway inflammation and pulmonary tissue remodeling resulting in a variety of clinical manifestations and treatment responses. Recent studies have shown an increasing appreciation of heterogeneity in asthma based on molecular phenotyping, biomarkers, and differential responses to therapies. In terms of asthma classification, perhaps the most important distinction to make is whether the patient has evidence of an eosinophilic inflammatory process characterized by type 2 immune response (Th2) or not. Therefore, personalized therapies to asthmatic patients just will be a reality by identifying and characterizing biomarkers. This review approaches the advances in diagnoses and management of asthma and severe asthma and highlights those with difficult-to-treat asthma based on each phenotype and biomarkers, to assist in the optimization of conventional therapy and to guide the use of targeted therapies.

Keywords: severe asthma, phenotypes, endotypes, biomarkers, therapy

1. Introduction: severe asthma definition

Asthma is a heterogeneous disease featured by the airway chronic inflammatory process associated with airway hyper-relativity due to direct and/or indirect stimuli such as exercise,

exposure to allergens or irritants, weather change, and respiratory infections. Asthma is characterized by wheezing, shortness of breath, coughing, chest tightness, and variable expiratory airflow limitation. These symptoms may vary over time and intensity and the symptom resolution and airflow limitation can occur spontaneously or in response to pharmacotherapy [1, 2]. The clinical classification of asthma is recent onset asthma, mild and severe forms, or even asymptomatic asthma [1].

The severe asthma (SA) concept is preconized by the European Respiratory Society–American Thoracic Society, which classifies severe asthmatic patients who require treatment with high-dose inhaled (or systemic) corticosteroids (ICS) in combination with a second long-term medication (long-acting β2 agonists—LABA). This definition includes patients who either maintain or are not in control of the disease [3, 4].

The first step to identify SA is to confirm if the patient presents the basic criteria for asthma itself, that is, reversible airway obstruction and bronchial hyper-reactivity and classic clinical symptoms such as wheezing, shortness of breath, cough, and chest tightness. However, many patients with SA do not meet these criteria as those ones with associated obstructive pulmonary disease and vocal cord dysfunction. After confirming the asthmatic condition, the second step is to determine the therapeutic control of the disease, which means adding ICS/LABA combination. However, some asthmatic patients remain poorly controlled independent of therapy leading to exacerbation of clinical symptoms and airway obstruction and might indicate severe and/or frequent asthma [5].

2. Severe asthma epidemiology

Asthma spreads all over the world, affecting more than 300 million people [2, 6]. This milestone makes it one of the most common chronic inflammatory diseases worldwide [5]. Based on standard methods for assessing the asthma symptoms, its global prevalence ranges from 1 to 16% of the population in different countries, while the asthma fatality rate is about 346,000 people around the world [2]. According to epidemiological data, asthma prevalence is higher in developed countries; however, it is also presented in countries with lower economic and social indicators, that is, developing countries [7], with a prevalence of 1%. Another aspect of this disease is the higher prevalence in urban areas in comparison with rural places [2]. Indeed, asthma prevalence has increased in the world over the past decades and is in a constant increasing rate [8, 9].

Asthma development is directly related to immunological factors, immediate hypersensitivity process, age, gender, and obesity. In an overview, around 50% of children under 3 years old and 80% over 6 years old who are diagnosed with asthma are atopic individuals [2, 10]. In most cases, asthma is an inconstant disease throughout the patients' lives, along which they may have periods of remission and asthma attacks [11, 12].

SA accounts for about 5–10% of all confirmed asthma cases in developed countries. Regarding the cost associated with the management of SA, it is about six times higher than the cost of

patients with mild-to-moderate asthma [1]. In addition, SA can come up concomitantly with other chronic diseases, such as rhinosinusitis and chronic obstructive pulmonary disease (COPD) [2]. Despite the high asthma prevalence worldwide, its pathophysiology, phenotypes, endotypes, biomarkers, and treatment still need to be elucidated, therefore, being of great interest of study for the scientific community [13].

3. Pathophysiology of severe asthma

The main pathophysiological feature of asthma is the bronchial inflammation resulting from interactions between airway structural cells and the innate/adaptive immune system. Structural cells of the lung, among them, epithelial cells, endothelial cells, and fibroblasts, release inflammatory mediators, mainly chemokines, and actively participate in the inflammatory process by attracting blood cells to the inflamed site. Thus, the development of the inflammatory response initially orchestrated by the lung structural cells in asthma also depends on innate immunity cells such as eosinophils, neutrophils, macrophages, mast cells, NKT cells, γδ-Tcells, inactive lymphoid cells (ILCs) and dendritic cells, and also on adaptive immunity cells represented by T and B cells. Interactions among these cells and the release of various inflammatory proteins, including cytokines, chemokines, adhesion molecules, eicosanoids, histamine, and nitric oxide (NO), promote the bronchial inflammatory process [14–16]. This inflammatory process is a common feature to all atopic asthmatic patients including those with the severe phenotype.

Histological addresses indicate that bronchial biopsies of asthmatic individuals reveal tissue structural changes, such as collagen deposition under the epithelium, which is described as the thickening of the basement membrane and of the smooth muscle layer of the airways due to the hyperplasia and the hypertrophy of the smooth muscle, which is most commonly observed in patients with severe asthma [17].

Further, there is an increase if the number of blood vessels (angiogenesis) in response to increased secretion of the vessel-endothelial growth factor (VEGF) [18] as well as an increase in mucus secretion commonly observed in biopsies of asthmatic patients, due to an increase in the number of secreting-mucus goblet cell in the epithelium and in the size of submucosal glands [19].

Once asthma presents a complex inflammatory process regulated by immune cells and structural bronchial cells collaborating for the initiation, exacerbation, and maintenance of the inflammatory process, all of these events might lead to irreversible bronchial structural changes and the airway remodeling which strongly contribute to severe development of asthma [15].

3.1. Airway remodeling

Airway remodeling can be defined as a set of changes in the composition, content and organization of the cellular and molecular constituents of the airway wall. The airway remodeling includes epithelial damage, cilial dysfunction, increased thickness of sub-epithelial basement membrane, angiogenesis, and neuronal proliferation. Also, it increases airway smooth muscle

mass and goblet cell hyperplasia with mucus production which causes stress and injury to epithelial cells [20, 21].

Epithelial damage is characterized by the thickening of the sub-epithelial basement membrane with deposition of collagens type I, III, V and VI, periostin, tenascin, osteopontin and fibronectin. Periostin is expressed in epithelial and matrix cells, upregulated by type 2 cytokines, and is implicated in the basement membrane fibrosis [22]. In addition, the epithelium is a source of members of the epidermal growth factor family (neurotrophins, angiogenic factors, and TGF-β) that promotes the neuronal and microvascular proliferation present in the airway remodeling. This process leads to mucosal fibrosis, muscle hyperplasia, and the reduction in distance between airway smooth muscle cells and the epithelium [20].

4. Phenotypes, endotypes and biomarkers

Traditionally, two clinical forms of asthma have been defined: allergic asthma and non-allergic asthma. About 80% of children and 50% of adults have allergic asthma characterized by an allergic sensitization defined by the presence of serum immunoglobulin E (IgE) and/or a positive allergy skin test for common proteins of inhaled allergens such as house dust mites, animal dander, fungal spores, plant pollen, or ingested allergens as peanuts. In 80% of the cases, patients with allergic asthma have concomitant allergic rhinitis. The "united airway disease" hypothesis proposes that allergic rhinitis and asthma are manifestations of the same underlying disease process and that each influences the severity of the other. Non-allergic asthma usually develops later in life with no IgE reactivity to allergens or any obvious involvement of the adaptive immune system such as Th2 cells. This form of disease is more common in women and it is often associated with chronic rhinosinusitis, nasal polyps, obesity, and is difficult to treat, often requiring long-term treatment with systemic steroids [15].

Currently, the division of asthma into only two clinical forms is oversimplified due to the discovery of diverse asthma phenotypes, each one with a distinct pathophysiology as better described further in this chapter. The asthma phenotypes differ in terms of genetic susceptibility, environmental risk factors, onset age, clinical presentation, prognosis, and response to therapies [23]; therefore, asthma is seen as a syndrome rather than a single disease [20]. It is also described as a considerable clinical overlap with COPD among smokers with asthma [2]. On the other hand, endotypes represent molecular mechanisms' underlying observable characteristics of phenotypes and characterization of mediators (biomarkers) as the pharmacological target for each phenotype is desirable to personalize each asthma syndrome [24, 25].

According to the spectrum of asthma, SA affects a group of patients with high medical needs, whose pathophysiology and clinical characteristics vary widely [7, 23]. Therefore, the clinical aspects of SA vary from those based purely on airway obstruction [13, 26] to those related to corticosteroid resistance [1, 3, 27] and to those based on life-threatening (or life-ending) diseases. Therefore it becomes sine qua non to classify SA by specific phenotype(s), endotype(s), and their biomarkers [28, 29].

4.1. Phenotypes of severe asthma

Phenotypes of SA involve a complex interaction of many genetic and environmental factors in association with observable characteristics, such as specific IgE responsiveness (biomarker) to particular allergens and lung functions [7, 23, 30] (**Figure 1**). Therefore, characterization of these phenotypes has involved biased and unbiased approaches to grouping clinical, physiologic, and hereditary characteristics [7, 31–33]. Nowadays, SA phenotypes are mainly composed of the following classification: type 2 asthma and non-type 2 asthma (**Figure 1**).

4.1.1. Type 2 asthma

Allergic asthma, which has been described as Th2 immune response (type 2), is a hallmark with an increase of $CD4^+$ T cells that produce IL-4, IL-5, and IL-13 detected on the bronchoalveolar fluid as well as on mucosal biopsies and correlated with blood and airway eosinophilia and

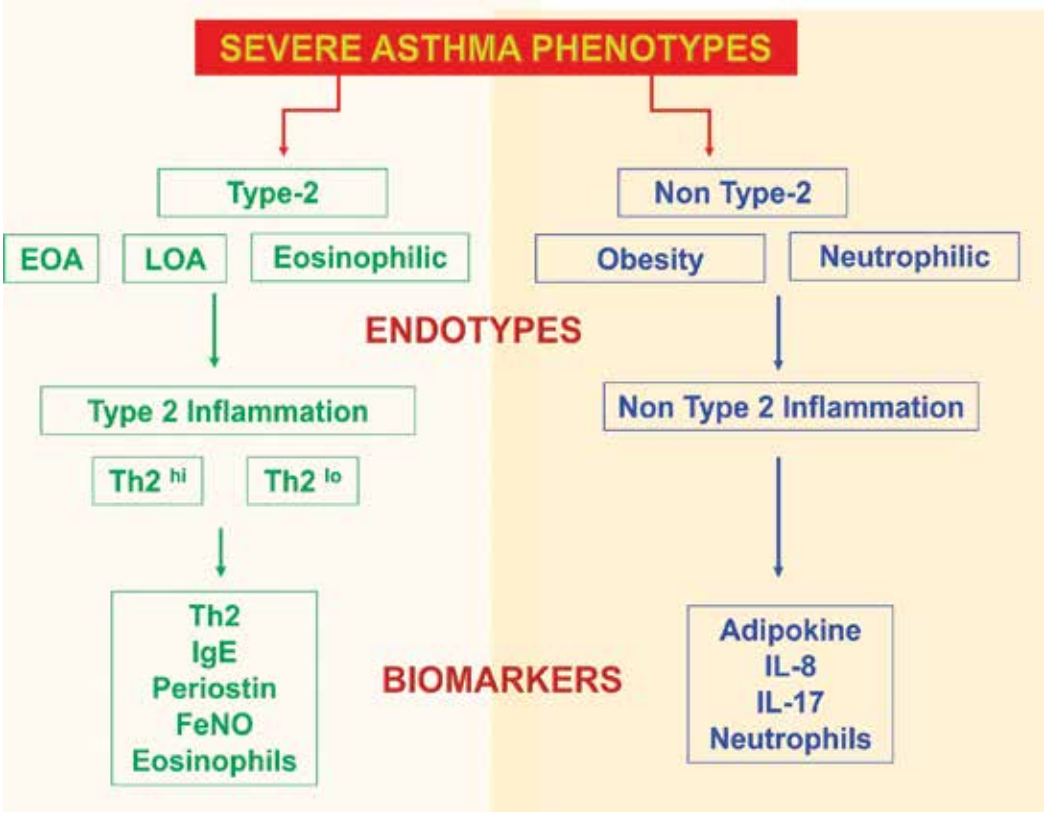

Figure 1. Phenotypes, endotypes, and biomarkers in severe asthma. Asthma is divided into phenotypes: type 2 inflammation and non-type 2 inflammation. Type 2 phenotype: early onset asthma (EOA), late onset asthma (LOA), and eosinophilic asthma; biomarkers: Th2 cytokines, IgE, Periostin, FeNO (fraction of nitric oxide expired), and eosinophilia. Non-type 2 phenotypes: asthma associated with obesity and neutrophilic asthma; biomarkers: adipokine, IL-8 or IL-17, and neutrophilia.

high-serum titer of allergen-specific IgE as biomarkers [34]. The presence or absence of these cytokines, allergen-specific IgE and eosinophilia, is a feature of $Th2^{hi}$ and $Th2^{lo}$ endotype clusters, respectively [35, 36]. The type 2 asthma phenotype is divided into early-onset asthma (EOA), late-onset asthma, and eosinophilic asthma [37].

4.1.1.1. Early-onset asthma (EOA)

EOA phenotype originates in early childhood, is characterized by an allergic component, and might be observed on the most asthmatic patients. However, the lack of responsiveness to corticosteroids and the lower concentrations of IgE in some children with asthma suggest that not all EOA is type 2-associated phenotype, and this may be important in the development of SA [38].

Recent researches have shown the importance of age at the onset to the SA phenotype [7, 13, 39]. Early onset better identifies "allergic asthma" than clinically available tests of atopy/allergy. Classification of adult asthma into EOA is widely used in the literature. A recent review included 12 studies comparing early- and late-onset current asthma in adults. The most common age used to delineate the 2 age-of-onset phenotypes was 12 years [40, 41]. EOA can be present with mild-to-severe disease, but it is unclear whether mild allergic asthma progresses to a severe disease or whether severe allergic asthma arises in childhood and remains severe [32].

The Severe Asthma Research Program (SARP) cluster analysis showed that people with the most severe EOA had greater numbers of skin-test reactions and poorer lung functions than individuals with mild asthma and that they were more likely to be of African descent. It also linked SA to a longer duration of disease and a history of pneumonia [42]. These data suggest that both genetic and environmental factors are important in asthma pathogenesis [13]. It is likely that as the severity of allergic early-onset type 2 asthma increases, non-Th2 immune pathways including those related to Th17 and Th1 are also engaged, as is innate immunity [43, 44].

The prognosis for children with initial severe atopic phenotypes is worse than for other phenotypes and this poor prognosis of allergic asthma with early onset has also been described in numerous prospective birth cohorts [23, 40]. In adults, mold sensitization in allergic asthma is associated with severe exacerbations requiring hospitalization and uncontrolled asthma despite high doses of ICS usage [13, 42].

4.1.1.2. Late-onset asthma

LOA is prevalent in adults over 65 and is also denominated as adult-onset asthma. The rate of morbidity and mortality of patients directly attributable to LOA is 4–15% higher than young patients with asthma [45, 46]. In addition, these numbers are underestimated due to the presence of comorbid diseases that complicate the diagnosis, as wheezing, breathlessness, and cough can also be caused by cardiovascular diseases [47]. The prevalence of asthma in the elderly is higher than was previously thought and considering the rapid aging of the global population the burden of asthma in the elderly is expected to rise significantly [15, 37]. In addition, older adults are more likely to be diagnosed with COPD without consideration of asthma, especially if they have a history of smoking [30]. Taking together these factors, the

differential diagnosis of asthma in adults is potentially more challenging than in children, and asthma costs may be higher among older patients due to increase of hospitalization.

The role of genetic predisposition in LOA is less clear than in atopic childhood-onset asthma. In LOA, a family history of asthma is often lacking and atopy is not more common than in the general population. Occupational asthma has become the most common type of LOA in many industrialized countries [48]. Forward, female sex hormones are associated with non-atopic LOA [49] whereas no sex difference was observed for the incidence of allergic asthma. Alternatively, asthma prevalence decreases with the number of years of oral contraceptive pill use [50]. In addition to that, there is evidence that the incidence of asthma decreases after menopause [51], whereas hormone replacement therapy in post-menopausal females is associated with an increased risk of asthma onset [52, 53].

Adult-onset asthma with highly elevated numbers of eosinophils often is related to sinusitis and nasal polyps. This phenotype indicates an association to type 2 cytokines and inflammatory cells such mast cells and basophils [54]. However, the lack of allergy clinical symptoms in this phenotype suggests that the Th2 process differs from and is probably more complex than the one associated with the early-onset asthma phenotype. As type 2 cytokines are also upregulated in cancer, inflammatory bowel disease, and interstitial fibrosis, a Th2 inflammatory process in the lung without mucosal-allergen-specific IgE and associated clinical allergic reactions is clearly possible [55, 56].

Also, some asthmatics present a mix of sputum neutrophilia and eosinophilia which might imply that there are interactions of additional immune pathways (endotypes) with Th2 immunity, including activation of pathways related to IL-33 and IL-17 by Th17 cells [57–59].

The phenotype named late-onset non-allergic asthma of the elderly [54] occurs in individuals beyond 65 years with a frequency of 8–10%. This phenotype can be grouped into two subphenotypes: (i) the persistent asthma and (ii) the newly diagnosed asthma [13, 20, 60] where atopy and elevated IgE levels are less frequent.

The physiologic and histopathologic findings in the airways of aging subjects are driven by important cellular age-associated changes. The immune system is complex and with increasing age, there are alterations in both the innate and adaptive immune responses, termed "immunosenescence." Research on this subject has focused primarily on cancer and autoimmunity but not in asthma. However, immunosenescence likely has important consequences in elderly asthmatics and increases susceptibility to airway infections, which in turn may exacerbate underlying SA or potentially play a role in the inception of LOA patients [22]. Another important issue in the airway of aging individuals is the increase in the number of sputum neutrophils [22, 26] and neutrophil mediators including MMP-9, neutrophil elastase, and IL-8, biomarkers for this phenotype, resembling changes seen in a phenotype of SA noted in some younger adults [1].

4.1.1.3. Eosinophilic severe asthma

Eosinophils are granulocytic effector cells that produce and store biologically active molecules, including cytotoxic proteins, that is, major basic protein (MBP), eosinophil peroxidase (EPX),

eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), lipid mediators, chemotactic peptides, as well as cytokines [61] against pathogens. However, the eosinophil-derived granule proteins are not only toxic to pathogens but also to other cells within immune responses, causing tissue damage and consequently organ dysfunction. In addition, eosinophils can contribute to inflammatory pathways through their capacity to synthesize and secrete a remarkable number of pro-inflammatory cytokines and chemokines [61–63].

Indeed, eosinophils produce type-2 cytokines (IL-4, IL-5, IL-13, and IL-25) and chemokines (CCL5/RANTES, CCL11/eotaxin, and CCL3) and are able to recruit leukocytes to the inflamed site [64, 44]. Alternately, following the allergen challenge, airway eosinophils have been shown to express GM-CSF and CXCL8/IL-8 [65, 66], thereby inducing neutrophil recruitment.

Therefore, eosinophils may contribute to airway remodeling in SA through release of transforming growth factor (TGFβ-1) [64]. It has also been reported that interferon-gamma (IFN-γ) might also potently activate eosinophils [67] and is elevated in the serum of some acute severe asthmatic patients [68], underscoring the importance of these pathways in SA.

Recently, a multiple-biomarker approach has been described to predict eosinophilic SA. These ones are represented by high-exhaled nitric oxide (FeNO) and elevated serum levels of periostin which correlate with increased eosinophil numbers in sputum, poor asthma control, and severe disease phenotype [69, 70]. FeNO is secreted by epithelial cells, macrophages, and other inflammatory cells in response to different stimuli into the asthmatic lung; however, the mechanisms involved in FeNO enhances still remain poorly unknown. On the other hand, periostin is mainly secreted by airway fibroblasts and epithelial cells in response to type 2 cytokines IL-4/IL-13 and TGF-β. Elevated levels of this biomarker have also been reported to correlate with eosinophil adhesion, recruitment and activation, airway remodeling, as well as chronic eosinophilic rhinosinusitis [70].

4.1.2. Non-type 2 asthma

Absence of type 2 profile in asthmatics represents half of all asthmatic patients and the lack of described biomarkers makes difficult phenotype-based therapy [71–73]. Some patients might lack type 2 inflammation profiles simply because corticosteroids have substantially reduced that pathway. Non-type 2 patients generally have LOA often in association with obesity, post-infectious, neutrophilia, smoking-related factors and are less likely to be atopic or allergic [7, 74].

4.1.2.1. Obesity-related asthma

Obesity and asthma are important public health problems [75], and the symptoms of asthma in obese individuals are more severe once these patients present development of steroid resistance, destabilization or lack of asthma control, and the worst quality of life [76]. Obese asthmatics are characterized in two phenotypes based in the Th2 profile: (i) an early-onset atopic asthma (EOA)—this phenotype presents $Th2^{hi}$ profile, where allergic asthma is complicated by the presence of obesity and (ii) late-onset non-atopic asthma (LOA)—this phenotype presents the $Th2^{lo}$ profile, occurring preferably in women and where the development of asthma is a consequence of obesity [77].

In the EOA phenotype, obese asthmatics have a history of atopy, increased airway obstruction, greater bronchial hyper-reactivity, higher IgE serum level, and a greater likelihood of allergic sensitization and reactions compared with late-onset obese asthmatics [78]. In contrast, late-onset obese asthmatics had less atopy, less bronchial hyper-reactivity, less airway obstruction, and fewer exacerbations [77]. There is a clear association between obesity and asthma and probably childhood obesity precedes the onset of asthma. However, more studies that clarify the characteristics of the two described phenotypes are needed [78].

Adiponectin is an important adipokine secreted by the adipocytes and its levels have been reported to be lower in obese patients [78]. In the asthma context, it appears that adiponectin does not protect against the development of inflammation and may in fact exacerbate the

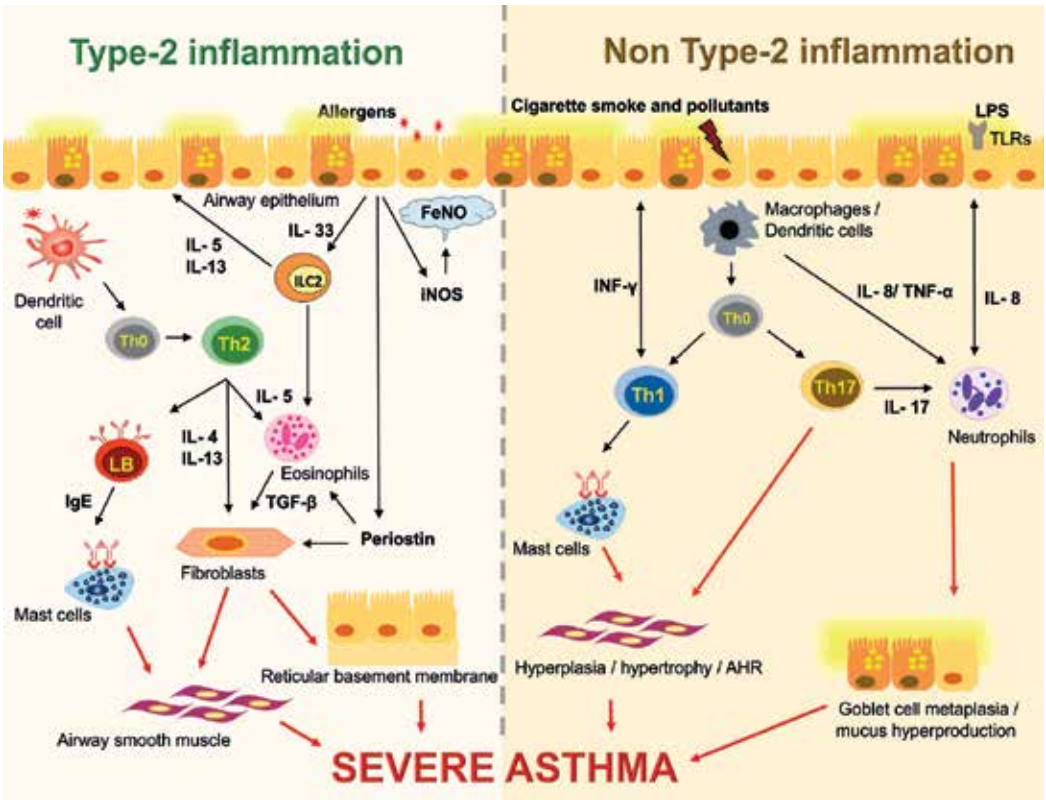

Figure 2. Type 2 inflammation and non-type 2 inflammation and its relation to structural changes in severe asthma. In type 2 inflammation, self-maintenance of the inflammatory process occurs through the following mechanism: Type 2 cytokines are generated by Th2. Lymphocytes and ILC2 cells, which activate several cells downstream, inducing remodeling of the airways through the thickening of the MBR, metaplasia/hyperplasia of goblet cells, mucus overproduction, and airway smooth muscle hyperplasia/hypertrophy. Factors involved in the development of non-type 2 inflammation in asthma include pollutants, cigarette smoke and microorganisms. These factors can activate innate immunity as well as Th1 and Th17 inflammatory processes. *Abbreviations*: AHR, hyper reactivity of the airways; FeNO, fraction of nitric oxide expired; IL, interleukin; ILC2, innate lymphoid cell; iNOS, nitric inducible oxide synthase; RBM, reticular basilar membrane; TGF-β, transforming growth factor-β; LPS, lipopolysaccharide; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

disease via anti-Th1 inflammatory effects, allowing type 2 differentiation and a more severe allergic response [75]. Another pro-inflammatory adipokine is resistin [29] whose levels of resistin: adiponectin ratio have been found to be higher in asthmatic uncontrolled subjects than in control subjects [78].

4.1.2.2. Neutrophilic asthma

Neutrophilia has been inconsistently associated with SA for several years although it is generally seen in corticosteroid-treated patients [79–81]. In affected individuals, lung neutrophilia has been associated with lower lung function, more trapping of air, thicker airway walls, and greater expression of matrix metalloproteinases compared to people with non-neutrophilic asthma; however, neutrophilia has not been associated with airway hyper reactivity [82, 83].

In SA, the number of neutrophils, in bronchi, is elevated compared to healthy subjects [58]. These cells were characterized by a high expression of the high affinity receptor for IgE (FcεRI) and released IL-8 (CXCL8) [84]. The expression of FcεRI on neutrophils seems to depend on the presence of type 2 cytokines [85]. The number of neutrophils in the airways of asthmatic individuals depends on IL-8 and TNF-α concentrations, both being chemotactic cytokines released from macrophages, epithelial cells, and neutrophils [86, 87].

Transcripts for IL17A were found to be elevated in the sputum of patients with asthma and were correlated with IL-8 transcripts and sputum neutrophils as well as with asthma severity [88]. Although, type 2 cells are predominant in the course of atopic diseases, the recruitment of neutrophils in the course of non-atopic asthma is driven by Th17—a subset of T helper cells releasing IL-17 [89, 90]. Neutrophilia can also coexist with eosinophilia, and this characteristic identifies people with disease severity and emphasizes the complexity of the immunobiology of SA in respect of the multiple different innate and adaptive immune pathways and cell functions involved in asthma phenotypes and endotypes [57, 91] (**Figure 2**).

5. Severe asthma management: classical and biological therapies

Several endotypes are targeted to control SA symptoms by reducing future asthma attacks. The most classical strategy to approach such outcomes in asthma pharmacological therapy is linked to regulation of the smooth muscle cell contraction/relaxation machinery. These targets are represented by an array of cell receptors reported as β2 adrenergic, muscarinic, and glucocorticoid receptors, phosphodiesterases enzymes, leukotrienes receptors, and leukotriene synthase enzyme [20]. These receptor functions are largely regulated by the classical pharmacological therapies used to treat asthma and they have been mentioned to cause a satisfactory disease control when administrated as monotherapy or in combination in different dosages for children, adolescents, adults, or special population which are the ones with comorbidities, that is, obesity, food allergy, anxiety, and depression and others [3].

Medications used for SA control and risk reduction so far represent the main strategy to attenuate the illness symptoms. In case of SA the combination of higher dose ICS and LABA

is recommended. These medications are pharmacologically classified as gold-standard steroid/bronchodilator drugs. Their effects occur by linking on nuclear cell receptors leading to strong inhibition of several inflammatory asthma parameters such as type-2 cytokine production, eosinophil activation, and mucus-secreting goblet cells, which are key components to asthma symptoms initiation, maintenance, and exacerbation [92, 93]. Also, the long-acting muscarinic agonist—LAMA named tiotropium—has been used as an add-on pharmacotherapy for SA control [94]. See below the main SA management medication/procedures in **Table 1**.

Adapted from [3].

However, classical pharmacological therapy causes side-effects and adverse drug events affecting for instance adrenal, growth suppression, and other organ malfunction [95]. Additionally, it has been reported that ≥40% of asthmatic patients are not well controlled which may require escalated treatment [96]. Therefore, new asthma targets/biomarkers have been searched in the perspective of improving asthma therapy considering the different disease endotype such as type 2, non-type 2, and bronchial epithelium-derived factors [28].

5.1. Endotypes/biomarkers-based asthma therapy

Anti-IgE therapy was previously described to treat SA patients that do not respond to classical therapy. High allergen-specific-IgE serum level has been reported as the type 2 asthma biomarker. Its secretion is crucial to eosinophil and basophil sensitization that is defined as a previous step to mast cell degranulation, and posterior pro-inflammatory and spasmogenic molecules stimulate smooth muscle cells, blood vessels, sensory nerves, and mucus-secreting goblet cells which are altogether pivotal to induce hyper-reactivity and lung inflammation [97]. Therefore, inhibiting IgE response is an important approach to control SA symptoms and in this perspective the anti-IgE medication omalizumab has provided good outcomes [98].

Treatment and strategies	Medication/procedure	Dosage
Higher-dose ICS/LABA combination	Prednisolone, formoterol	ICS: Max 2000 mcg/day LABA: Max. 72 mcg/day
Oral corticosteroids	Prednisone or prednisolone	Adults: 1 mg/kg/day Children: 1–2 mg/kg/day
Add-on therapy without phenotyping	Tiotropium (LAMA)	5 μg, 2.5 μg or 1.25 μg once daily during 4–week period
Add-on therapy with phenotyping	Omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5)	Omalizumab: 150–1200 mg once every 2 or 4 weeks Mepolizumab: 750 mg once every 4 weeks Reslizumab: 3 mg/kg every 4 weeks up to 24 months
Non-pharmacological therapy	Bronchial thermoplasty, high-altitude treatment and psychological interventions	

Table 1. Severe asthma management.

Therapy based on anti-IL-5 administration, mepolizumab, has been shown effective to reduce severe eosinophilic asthma symptoms by inhibiting IL-5 actions highly on eosinophils but also in basophil cells [61]. It is well documented that IL-5 is a key cytokine implicated in maturation, activation, proliferation, and survival of eosinophils. Then, part of difficult-to-treat eosinophilic asthma patients does not respond to both ICS and systemic glucocorticoids, which points to IL-5 as an important biomarker to be targeted in SA therapy. Also, a placebo-controlled trial in patients with eosinophilic severe asthma has revealed the safety and efficacy of the anti-IL-5 therapy named reslizumab which reduces asthma exacerbation and improves lung function as asthma control [99].

Another endotype-based therapy for SA has emerged and the use of anti-IL-4 and anti-IL-13 therapies indicates satisfactory outcomes [41]. Both cytokines present a crucial role in IgE synthesis, eosinophil activation, mucus secretion, and airway remodeling indicating that neutralizing these biomarkers might collaborate to SA control. Additionally, prostaglandin D (PGD) 2 receptor expressed by type 2 cells named CRTH2 has been implicated in SA symptoms which might be controlled by the use of a CRTH2 antagonist. PGD2 is an arachidonic acid derivative mainly secreted by mast cells and activates several cells. In response to activation, these cells secrete an array of pro-inflammatory cytokines present into the asthmatic lung [100].

Besides classical pharmacological and/or biological asthma therapy, other therapies (i.e., allergen immunotherapy, vaccinations, bronchial thermoplasty, and vitamin D), non-pharmacological treatments (i.e., avoidance of allergens, air pollutants, some foods and medicines, healthy diet, physical activity, weight reduction, dealing with emotional stress, and others), and complementary and alternative medicine have been reported in the literature. However, the last one has been not recommended for use by severe adult asthmatic patients due its limited evidence of effectiveness [101].

Individualized management protocol should be taken into account for asthmatic special population, for instance, exercise-induced bronchoconstriction in adolescents, elderly, pregnant, and aspirin-exacerbated respiratory disease; however, the management of SA is importantly challenging and the endotype-based therapies might be the better strategy to approach the illness control.

6. Conclusion

Human severe asthma is a heterogeneous disease and an emerging health public issue affecting hundreds of million people worldwide and such a complex inflammatory condition which has led this to be classified as a syndrome. Recent cluster analyses on severe asthma based on phenotypes, endotypes, and biomarkers have hardly classified this illness to better improving its management. Updated asthma phenotypes known as type 2, non-type 2, eosinophilic, or neutrophilic raise the necessity of new biomarker identification, mainly a single one, for diagnosis and therapy purposes. In this chapter, we reviewed the advances on severe asthma phenotypes/endotypes, diagnoses, and management based on classical medication composed of high doses of inhaled corticosteroids and long-acting β2 agonist combination as well as

those add-on therapies represented by long-acting muscarinic agonists, biological/monoclonal antibodies, and non-pharmacological approaches routinely used to control difficult-to-treat asthma. Finally, taking all these new concepts and management strategies on severe asthma, it has been agreed by international consensus on the urgent need for the development of a new phenotype/endotype-based therapy to treat severe asthma.

Author details

Marcia Regina Piuvezam[1]*, Laércia Karla Diega Paiva Ferreira[2], Talissa Mozzini Monteiro[2], Giciane Carvalho Vieira[3] and Claudio Roberto Bezerra-Santos[1]

*Address all correspondence to: mrpiuvezam@ltf.ufpb.br

1 Department of Physiology and Pathology, Federal University of Paraíba, João Pessoa, Paraiba, Brazil

2 Federal University of Paraíba, João Pessoa, Paraiba, Brazil

3 Department of Morphology, Center of Health Science, Federal University of Paraíba, João Pessoa, Paraiba, Brazil

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Chapter 9

Monoclonal Antibodies for Asthma Management

Dolly V. Rojas, Diana L. Silva and Carlos D. Serrano

Additional information is available at the end of the chapter

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Abstract

Asthma is a multifactorial and complex disease, with different degrees of risks and severity, as well as the response to treatment. Medications currently available are most effective in severe asthma; nonetheless, there is a percentage of patients that have no response to the treatment that guidelines suggest in their recommendations. In the last years, there have been new insights in inflammatory molecules that contribute to asthma physiopathology and a lot of them have been considered to be possible targets in the management of severe asthma. As a consequence of this, a few monoclonal antibodies have been developed evidencing their effectiveness in the treatment of the disease. The study of these new therapies has allowed the identification of specific inflammatory pathways. This chapter intends to offer a critical perspective of the current guidelines for the management of severe asthma, as well as to discuss current treatments and the future on new molecules. Through an adequate characterization, different phenotypes will be recognized and associated with a determinate biomarker and should be used to select the treatment that can offer the highest efficiency in these patients. In this way, the treatment will be directed to a personalized medicine.

Keywords: severe asthma, inflammation, phenotype, treatment, monoclonal antibodies

1. Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. The GINA guidelines indicate that inflammation control is a key for management goals and as such is considered a treatment priority. Severe asthma represents a good part of the health spending, with significant impact on patients' quality of life. Hence, the identification and correct treatment of severe asthma may help to control exacerbations and the inflammatory process, thus improving the personal, social, and economic impact of the disease [1]. In the

pathophysiology of asthma, there are multiple processes mediated by various cytokines and cells that cause inflammation. Management goals have been directed toward these molecules and cell targets through the use of corticosteroids, which have meant a dramatic change in the control of the disease. However, these drugs act in a nonspecific way. Furthermore, the development of new monoclonal antibodies could represent a significant milestone for treatment of asthma, reinforcing the essential idea of personalized medicine. In 1984, researchers Jerne, Köhler, and Milstein received the Nobel Prize in Medicine for their work on plasma cell and multiple myeloma cell fusion, which allowed the generation of specific antibodies with the appropriate genetic information, but at high speed. In subsequent years, immunoglobulins synthesized from this new technology, with specific target molecules, such as the endotoxin of Gram-negative bacteria in sepsis, demonstrated an initial benefit. Subsequently, the concept of personalized medicine began to take shape, and in recent years, biomedical research has focused on deepening the molecular mechanisms underlying various pathologies, parallel to the production of new drugs that act at crucial points of specific immunological cascades. Therefore, monoclonal antibodies are an effective and safe therapeutic alternative in many chronic diseases such as rheumatoid arthritis, cancer, and asthma and are seen as a hopeful option in many other diseases. The challenge now is not to get lost in the wide variety of clinical studies that can be found in the literature, as well as in connecting a particular patient with the appropriate management based on the evidence.

2. Critical view of current guidelines and treatment

Large studies on severe asthma have expanded our knowledge about the characteristics of the disease. Severity is defined as the requirement for systemic corticosteroids more than twice a year, the need for at least one hospitalization, previous admission to an intensive care unit, the need for mechanical ventilation in the previous year, impaired pulmonary function determined by a forced expiratory volume in the first second (FEV1) less than 80% of the predicted in the presence of forced vital capacity (FVC) below normal limits after the administration of bronchodilator, or the use of high doses of corticosteroids inhaled and long-acting beta-2-agonists without achieving control of symptoms [2]. In fact, it is estimated that 50% of patients are not well-controlled despite receiving optimal treatment, and that 5–10% do not respond to treatment. Also, receiving high doses of inhaled or systemic corticosteroids increases the risk for adverse effects, which implies an affectation of the additional quality of life due to the sum of other secondary diseases [3]. The GINA guidelines include evidence-based diagnostic and therapeutic recommendation derived from studies that meet all criteria of scientific validity. However, it is possible that in selected patients, guidelines do not accurately reflect what a clinician is trying to address.

The guidelines suggest management according to severity and control, symptom dynamics and pulmonary function, but these are directed to the total population of patients with asthma [1]. In this sense, there will always be a percentage of patients who either receive a suboptimal treatment or who remain unresponsive despite being in the most serious step. Finally, the guidelines are not based on the characteristics of the specific inflammation related to the different phenotypes, which are the ones that could define with greater precision what

would be the ideal treatment to stop a specific pathophysiological mechanism [4]. It is not sufficient then to establish a management based only on severity, since there are several aspects that arise from the very concept that asthma is a heterogeneous disease and with different molecular and genetic bases, so if a patient should be typecast within a general parameter, reduce their therapeutic options [5]. On the other hand, the control of severe asthma represents a challenge for specialists in allergology and pneumology due to the high impact of this disease on the quality of life of patients. The GINA guidelines establish levels of disease control according to the response to treatment as follows: well-controlled, partially controlled, and uncontrolled. However, it can differ as patients cataloged in one of the degrees, in reality corresponding to another, taking into account that probably a partially controlled asthma is actually an uncontrolled asthma and that this has therapeutic implications. In daily practice, middle terms cannot be established to define management. Some patients persist without control despite established therapeutic recommendations, which allows us to infer that as with severity, there are other aspects that should be evaluated from the pathophysiology of the disease and not only based on the degree of control of the disease. Additionally, the classification based on control is very strict and poorly documented.

2.1. Approach by phenotypes

It is clear that some characteristics can be identified in some asthmatic patients and not in others; from this arises the concept of "phenotype," which is defined as the presence of different characteristics that are the product of the interaction of genes with the environment. There may be overlap between them and that the same patient can migrate transiently or definitively from one phenotype to another. The challenge, therefore, is to determine in each patient the individual characteristics.

Several years ago, Chung and Adcock [6] published a review about phenotyping of asthma. The first systematic study of severe asthma carried out in Europe by the group ENFUMOSA (European Network for Understanding Mechanisms of Severe Asthma) [7] consolidated the concept that asthma has a heterogeneous expression, and thus, severe asthma should be considered a different form of the disease, more than simply an increase in the symptoms of it. Subsequent studies included in the Severe Asthma Research Program (SARP) of the United States, together with the results of the ENFUMOSA group, and subsequently of the BIOAIR (Longitudinal Assessment of Clinical Course and BIOmarkers in severe chronic AIRway Disease) [8], have extended the knowledge of clinical expressions and generated new hypotheses about the pathophysiology of severe asthma. In this way, five phenotypes have been established:

1. Early onset atopic asthma with airway dysfunction, eosinophilic inflammation, and high number of hospitalizations.
2. Asthma with noneosinophilic inflammation, obesity, and present in the female sex.
3. Early onset asthma, with few symptoms and minimal eosinophilic inflammation.
4. Asthma with eosinophilic inflammation, with few symptoms and delayed onset.
5. Asthma with neutrophilic inflammation.

2.1.1. Severe asthma early onset

It comprises 40% of all severe asthmatics. Patients develop the disease in childhood and have a history of atopy, increased bronchial hyperresponsiveness, higher levels of total immunoglobulin E (IgE), and a higher eosinophil count both peripherally and in sputum, as well as a tendency to subendothelial fibrosis and overexpression of the mucin gene. In general terms, they respond to management with inhaled corticosteroids. Family history suggests a genetic component; in fact, multiple studies have reported associations between genes related to the expression of the Th2 phenotype and multiple polymorphisms related to greater severity. The Th2 pattern of cytokines, including interleukins (IL) 2, 4, 5, 9, and 13, is expressed in the bronchial submucosa of these patients. These cytokines contribute to the allergic inflammation of the airway, generating the activation and the recruitment of B lymphocytes producing specific IgE, mast cells, basophils, and eosinophils. IL-13 also acts as an inducer of the genes of regulator 1 of the chlorine channels, periostin, and the inhibitor of serpin peptidase.

Recently, the role of thymic stromal lymphopoietin (TSLP) has been described as an inducer of IL-4, -5, and -13 production in the initiation of cellular response mediated by Th2 pattern cells, as well as IL-25 and -33, which are produced in response to exposure to allergens, contaminants, and viruses. IL-33, which is a member of the cytokine family of IL-1, possesses potent induction and chemotactic activity of Th2 lymphocytes. Elevated levels of IL-33 and TSLP have been observed in patients with asthma, especially in severe cases [9].

2.1.2. Phenotypes with and without eosinophilia

An increased presence of eosinophils in induced sputum and in peripheral blood can identify the eosinophilic subgroup. The cutoff points are at least 3% of eosinophils in the sputum and peripheral eosinophilia greater than 350 (absolute number). The noneosinophilic phenotype has been defined as asthma with eosinophils in induced sputum less than 3% and increased neutrophilic infiltration. The mechanisms that explain neutrophilia in the airway are not very clear. It has been suggested that this phenotype reflects a "non-Th2" pattern with all its molecular implications. In addition, it is associated with a poor response to treatment with inhaled corticosteroids (even inducing even more neutrophilia), suggesting a Th1 pattern orchestrated by the tumor necrosis factor alpha (TNFα), which is assumed to have an important role. Both Th17 cells and bacterial colonization of the airway secondary to defects in phagocytosis have been implicated as causes of neutrophilia [10].

The identification of phenotypes results in a large number of treatments with specific objectives, which have been developed for some years. The challenge is to unify the physiopathology with clinical phenotypes and use that knowledge to discover other phenotypes that have not yet been recognized. None of the clinical phenotypes established to date has a detailed identification of their pathophysiology, biomarkers, genetic elements, stability over time, or the response to a specific treatment. Probably, all the factors that influence a phenotype will need to be incorporated into an endotype, which is nothing else than the subtype defined by the functional or pathophysiological mechanism of the disease for a particular individual.

The support of the evidence regarding the conformation of phenotypes and endotypes continues to be limited by the lack of large-scale longitudinal studies that may intertwine the

pathophysiology with the clinical findings. However, there are already phenotypes that seem to be clearly defined in terms of their clinical and molecular bases, and in which the pharmacological intervention with monoclonal antibodies constitutes an important starting point in the management of severe asthma [2].

3. Monoclonal antibodies

Monoclonal antibodies are specialized glycoproteins produced by B cells from a stem cell, forming identical clones of it. They can recognize specific molecules, such as cytokines or receptors.

3.1. Chimeric monoclonal antibodies

They are artificial molecules in which the constant portions of the heavy and light chains come from a human immunoglobulin and the variable regions VL and VH (variable region of the light and heavy chain, respectively) are obtained from an antibody of murine origin. The goal with the construction of a chimeric antibody is to reduce immunogenicity without affecting the selectivity of the antibody for the antigen. These molecules have 66% of human component and 33% of murine origin; they are less immunogenic than the first-generation monoclonal antibodies, but they can still induce an immune response against them. Antibodies of this type end with the prefix ximab (e.g. infliximab, rituximab).

3.2. Humanized antibodies

These molecules have 90% of human origin, so when it is injected into the patients, there is no response from the immune system. Only the antigen binding site (paratope) is of murine origin and is formed from the spatial combination of the hypervariable loops. The rest of the variable region (called M) only works as a scaffold whose function is to serve as structural support to the paratope. In this way, the epitopes associated with the murine M regions, which are present in the chimeric antibodies, are not found in the humanized antibodies. This type of antibody ends with the prefix zumab (e.g., omalizumab, trastuzumab).

3.3. Human antibodies

Almost 100% of its structure is human. However, while the production of mouse monoclonal antibodies is routinely carried out by hybridoma technology, the production of human monoclonal antibodies by this technology has been difficult, because the human hybridomas and cell lines derived from multiple myeloma have been difficult to develop and immunization in vivo is not feasible for many antigens. However, several techniques make it possible to generate human monoclonal antibodies, such as the expression of immunoglobulin fragments, the single-chain variable fractions, and the single strands of the variable fraction. Currently, the development of recombinant monoclonal antibodies by phage library technology with genes that encode the immunoglobulin variable regions has proven useful in basic and clinical research. This type of antibody ends with the prefix mumab or numab (e.g. adalimumab, secukinumab) [11–13].

The traditional production process of monoclonal antibodies is outlined in **Figure 1**.

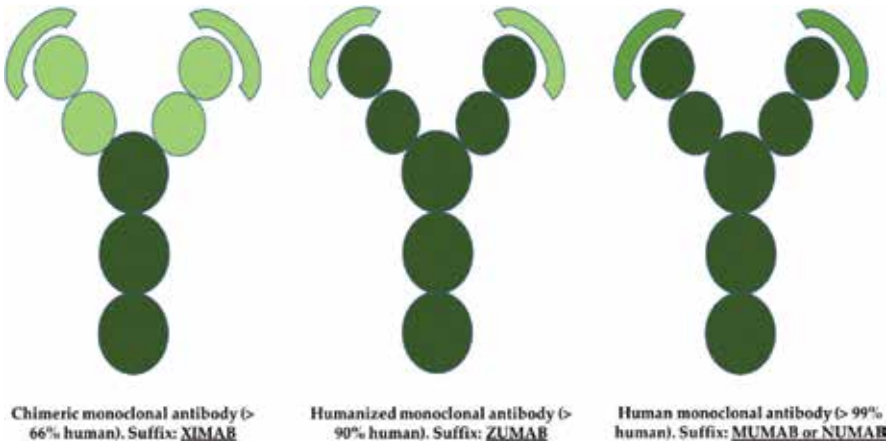

Figure 1. Types of monoclonal antibodies according to their humanization.

3.4. Development and production

The production of monoclonal antibodies is based on the method of fusion of B lymphocytes from an immunized animal (usually a mouse), with an immortal myeloma cell line and the culture of the cells in a medium in which the nonfused normal and tumoral cells cannot survive. The resulting fused cells that are obtained are called hybridomas and each hybridoma produces only one immunoglobulin, derived from a B lymphocyte of the immunized animal [11]. The method as such consists of the fusion of spleen cells from a mouse immunized to an antigen or mixture of known antigens, with a myeloma cell line, with the subsequent formation of hybrid cells that preserve many chromosomes of the fused pairs. These cells are then placed in a selection medium that allows the survival only of immortalized hybrids, which in turn are cultured as cell clones that secrete the antibody of interest. This method of selection includes hypotaxine,

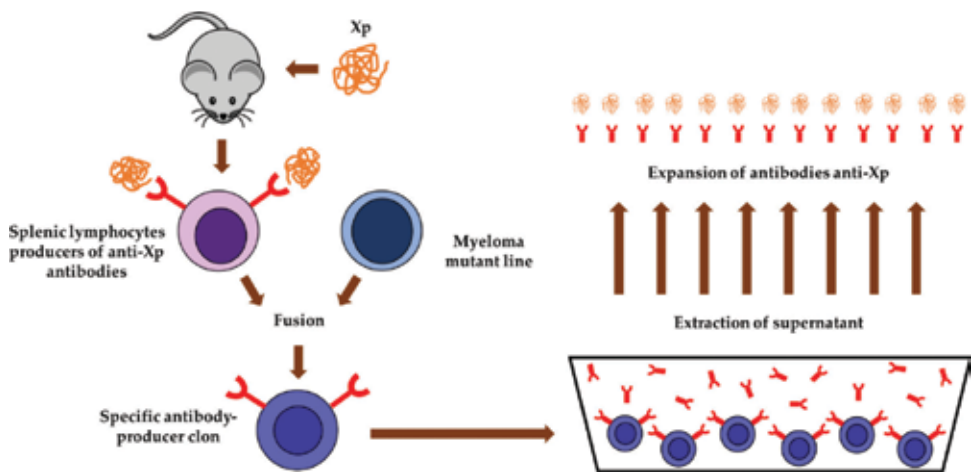

Figure 2. Schematic process for the production of monoclonal antibodies. Xp: "X" protein.

aminopterin, and thymidine, and is therefore called HAT [14]. Antibody-producing hybridomas are expanded in larger capacity culture vessels, and the cells are harvested by centrifugation, suspended in culture medium supplemented with fetal calf serum and dimethyl sulfoxide (DMSO) to freeze, first at −70°C and then in liquid nitrogen. The production of the monoclonal antibody is made from the supernatant of bulk cultures or after intraperitoneal inoculation of the hybridoma in histocompatible animals. In the latter case, an antibody-producing tumor is produced that generates an ascitic fluid rich in these. In both cases, the monoclonal antibodies are separated and purified by conventional methods [15] (**Figure 2**).

4. Current and future targets in the management of asthma

4.1. Current targets

4.1.1. Nonspecific blockade of inflammation (corticosteroids and leukotriene antagonists)

At present, asthma control focuses on the use of inhaled corticosteroids, either alone or in association with leukotriene antagonists, and/or long-acting beta-2 agonists. Numerous studies have documented the efficacy of corticosteroids in reducing inflammation, both in children and adults and at any degree of severity. Currently, they are considered the most effective drugs to achieve control in most cases. Its action requires binding to a cytoplasmic receptor (alpha GR), which is associated with heat shock proteins (Hsp90-Hsp60). The binding of the corticoid to its receptor induces the dissociation of these proteins and the translocation of the complex toward the nucleus where several events occur that lead to the activation of the transcription of anti-inflammatory genes and the blocking of those pro-inflammatory. Additionally, corticosteroids interact directly with transcription factors, such as the nuclear factor kB, further blocking the expansion of the inflammatory process.

The use of these drugs has made it possible to reduce both the symptoms and the frequency and severity of the exacerbations, improving quality of life, lung function, and reducing bronchial hyperreactivity. However, their lack of specificity makes them susceptible to generating adverse effects in different organs. In addition, there is a percentage of patients resistant to corticosteroids, a phenomenon explained, among other causes, by the presence of a receptor isoform unable to bind to the glucocorticoid [16].

It is difficult to know if in the medium or long term, corticosteroids will continue to be the standard asthma therapy. Likewise, it is uncertain whether the advent of monoclonal antibodies will allow the reduction of the dose of corticosteroids and/or their total clearance in patients with severe asthma. The cysteinyl leukotrienes comprise C4, D4, and E4 leukotrienes. They are mediators that play an important role in inflammation, mucus secretion, bronchospasm, and remodeling. The antagonists of the type 1 receptors of cysteinyl leukotrienes (montelukast) are potent and selective and block their action in a competitive manner, generating an interruption of the pro-inflammatory intracellular cascade with a subsequent reduction of its effects. Clinical studies show that antagonism of these receptors is beneficial to some degree and percentage of the population. However, it is never superior to the effects

achieved with corticosteroids used as monotherapy or in combination with long-acting beta-2 agonists. The precise indications for use in asthma have not been completely defined. It seems that its administration in transient early wheeze triggered by virus and without atopy works to a certain extent [17].

4.1.2. Long-acting β-agonists (LABA) combined

The agonist stimulation of the beta 2 adrenergic receptors generates smooth muscle relaxation of the central and peripheral airways, reversing the bronchial obstruction in asthmatics. The effect is given by the activation of adenylate cyclase (it catalyzes the conversion of adenosine triphosphate—ATP—into cyclic adenosine monophosphate—AMPc), generating the decrease in intracellular calcium, and thus causing muscle relaxation. This treatment always associated with a corticoid is a choice when control is not achieved with the inhaled corticosteroid alone [18].

4.1.3. Anti-IgE therapy

IgE is a clear therapeutic goal in allergic diseases. It is released by the plasmocyte, binds to its receptor of high affinity in the mast cell, and later, upon exposure to the allergen involved, induces several effector responses including the release of mediators responsible of allergic reaction. Omalizumab, a recombinant humanized monoclonal antibody, binds specifically to free serum IgE in its CH3 domain, near the high-affinity receptor binding site, thereby blocking its interaction with mast cells, basophils, antigen-presenting cells, and other inflammatory cells that express the receptor. That binding results in the decrease of free IgE, generating a negative feedback of the receptor of high affinity, and therefore, an interruption of the inflammatory cascade evident by the reduction of the levels of tissue eosinophils and peripheral blood, as well as of the GM-CSF, and IL-2, -4, and -13. They also decrease the presentation of allergens to T cells and the production of cytokines that stimulate differentiation toward the Th2 phenotype [19] (**Figure 3**).

The efficacy and safety of omalizumab treatment in severe asthma has been demonstrated in several controlled studies, showing a significant reduction in exacerbations, a steroid-sparing effect, and improvement in quality of life. The greatest benefit has been observed in patients with allergic asthma, particularly those of greater severity, who failed to respond to conventional treatment [20]. Since 2003, this continues to be its main indication, when it was approved by the Food and Drug Administration (FDA). In 2005, it was approved by the European Medicines Agency (EMA) as an additional therapy in adult patients and in children older than 6 years with persistent severe uncontrolled allergic asthma, with decreased lung function (FEV1 less than 80% of predicted), despite the chronic management with high doses of inhaled corticosteroids plus long-acting beta 2-agonists and with evidence of sensitization to at least one aeroallergen in the skin test or by determination of specific IgE in blood [21]. In Colombia, Invima has approved it since 2005 with the same indication.

4.1.4. Interleukins 4 and 13

IL-4 and -13 are considered the most important cytokines in allergic inflammation in the respiratory tract for a long time; they are essential for the differentiation of CD4+ lymphocytes toward the Th2 phenotype. In addition, they are the promoters of the Ig class switch toward the production

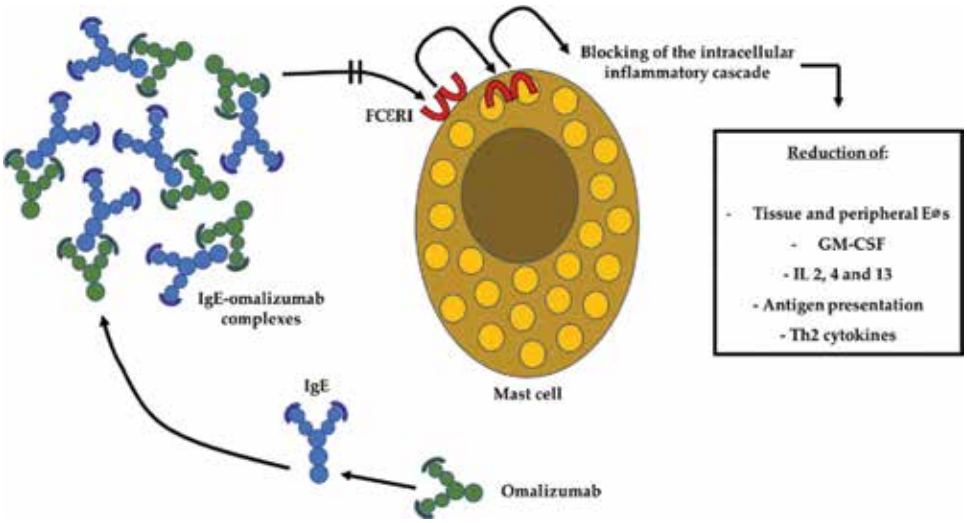

Figure 3. Molecular effects of omalizumab. This antibody binds to soluble immunoglobulin E (IgE), preventing its binding to the high-affinity receptor on the mast cell membrane. This generates a negative feedback that induces the internalization of this receptor and the blockade of the entire intracellular inflammatory cascade with the subsequent anti-inflammatory effects. FCεRI: high-affinity receptor for IgE; Eøs: eosinophils; GM-CSF: colony-stimulating factor of granulocytes and monocytes.

of IgE, of the differentiation of the B cells in plasma producing specific Ig E, and of the recruitment of eosinophils to the airway through the receptors for them that are expressed in them. They also stimulate mast cells and other pro-inflammatory cells. IL-13 favors the development of airway fibrosis and mucus hypersecretion, and in conjunction with IL-4, induces inflammation, remodeling, and the proliferation of bronchial fibroblasts and smooth muscle cells [22].

4.1.5. Interleukin 5

It is produced mostly by Th2 cells, mast cells, basophils, and eosinophils. This cytosine mainly conditions the population of eosinophils, from their medullary differentiation to their maturation, survival, and activation. It is a potent inhibitor of eosinophilic apoptosis [23].

4.2. Future targets

4.2.1. Interleukin 9

It is produced by Th2, Th9, basophil, eosinophil, and mast cells, and is thought to be also by neutrophils. This cytokine acts by binding to its IL-9R alpha receptor, generating an increase in the proliferation and attraction of mast cells. It plays a very important role in the differentiation and activation of Th2 cells. Together with interleukins 4 and 13, it acts on the smooth muscle and the airway epithelium, contributing to bronchial hyperreactivity [23].

4.2.2. Granulocyte macrophage colony-stimulating factor

It is a growth factor involved in the differentiation and survival of eosinophils [23].

4.2.3. Thymic stromal lymphopoietin

It is an epithelial cytokine similar to IL-7, produced in response to a pro-inflammatory stimulus. It acts by inducing the release of cytokines from the Th2 pattern. Patients with asthma have elevated levels of this cytokine in their airway, showing a correlation between the degree of elevation and the severity of the disease. In fact, several studies have shown that some polymorphisms in the locus for the TSLP gene have a protective effect for the development of asthma and bronchial hyperreactivity [24].

4.2.4. Prostaglandin D2 receptor (PTGDR)

It is a receptor located in Th2 cells, innate lymphoid type 2 cells (ILC2), and in eosinophils. Prostaglandin D2 is its natural ligand. PTGDR activation stimulates the synthesis of Th2 cytokines.

4.2.5. Interleukin 25

It is produced by epithelial cells in response to different stimuli. Through the induction of GATA 3, it favors the differentiation toward Th2 and ILC2 cells. It has an essential role in inflammation of the airway and in the remodeling process [25].

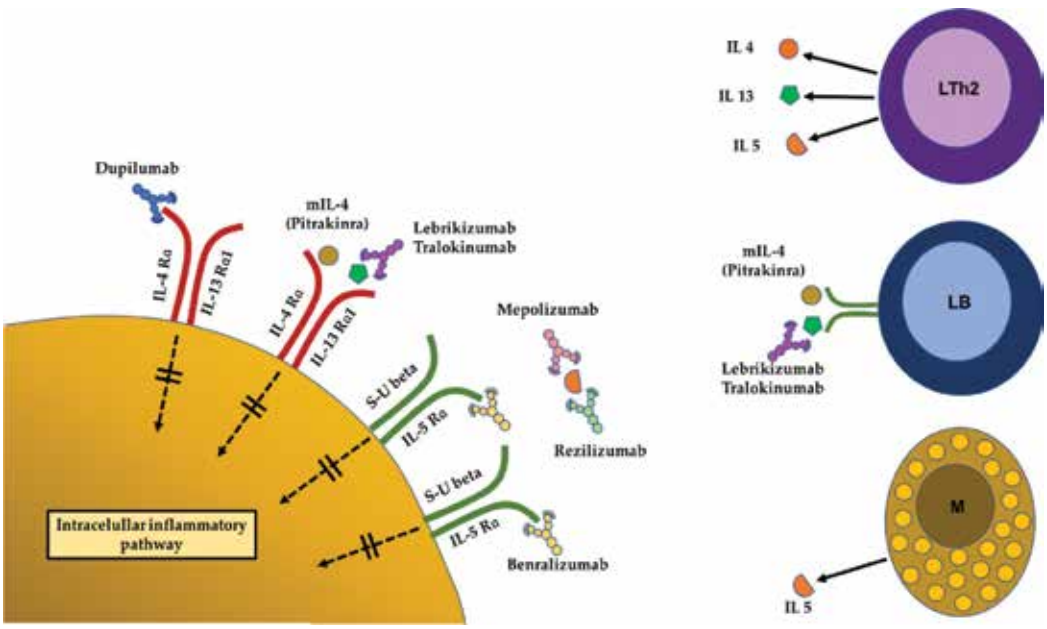

Figure 4. Different monoclonal antibodies with their respective therapeutic targets within the inflammatory cascade of asthma. The neutralization of the different receptors and mediators blocks the intracellular cascade of kinases that amplify the inflammatory process. IL-4Rα: alpha receptor for interleukin 4; IL-13 Rα1: alpha 1 chain of the interleukin 13 receptor; rIL-4: inactive recombinant interleukin 4; S-U: subunit.

Antibody (references)	Type	Target	Study phase	Clinic outcomes	Inflammatory outcomes	Dose/route/interval
Benralizumab [27–31]	Humanized	IL-5Rα	II–III	- Reduction of exacerbations, and hospitalization - Improvement of FEV1 - Improvement of the quality of life	- ↓ eosinophilia - ↓ sputum eosinophils - ↓ECP	20–100 mg SC/4–8 weeks
Mepolizumab [32–35]	Humanized	IL-5S	II–III	- Reduction of exacerbations - Reduction of dose of oral corticosteroids - Improvement of the ACT - Improvement of FEV1	- ↓ eosinophilia - ↓ sputum eosinophils	75 mg IV/month 100 mg SC/month
Reslizumab [36, 37]	Humanized	IL-5S	III	- Improvement of FEV1 - Improvement of the ACT - Improvement of symptoms - Reduction of exacerbations	- ↓ sputum eosinophils	3 mg/kg IV/month
Dupilumab [38, 39]	Human	IL-4Rα	II–III	- Reduction of exacerbations - Improvement of FEV1 -Improvement of the quality of life	- ↓ FeNO - ↓ total IgE - ↓ eotaxin 1	200 mg SC/2 weeks
Pitrakinra [40, 41]	rIL-4	IL-4Rα	II	- Reduction of exacerbations* - Reduction of night awakenings* - Reduction of activities limitation by asthma* - Reduction of exacerbations in patients with eosinophilia - Reduction of need for beta-2's rescue -FEV1 improvement	- ↓ FeNO	3–10 mg inhaled/12 h

Antibody (references)	Type	Target	Study phase	Clinic outcomes	Inflammatory outcomes	Dose/route/interval
Lebrikizumab [42, 43]	Humanized	IL-13	II–III	- Reduction of exacerbations - Improvement of FEV1	- ↓ periostin	125–250 mg SC/month
Tralokinumab [44, 45]	Human	IL-13	II–III	- Reduction of bronchial hyperreactivity - Reduction of need for beta-2's rescue - Improvement of FEV1	- ↓ eosinophilia	300 mg SC/2–4 weeks

*Defects associated with specific polymorphisms. Other monoclonal antibodies that have been studied: anti-TSLP [46]; enokisumab (anti IL-9) [47]; anti-GM-CSF [48]; anti IL-25 [49]; anti IL-33 [50].

rIL-4: inactive recombinant interleukin 4; IL-5Rα: alpha receptor for interleukin 5; IL-5S: soluble interleukin 5; IL-4Rα: alpha receptor for interleukin 4; IL-13: interleukin 13; FEV1: forced expiratory volume in the first second; NS: not significant difference; ACT: asthma control test; ECP: eosinophilic cationic protein; FeNO: expired fraction of nitric oxide; IgE: immunoglobulin E; SC: subcutaneous route; IV: intravenous route.

Table 1. Main monoclonal antibodies that have been studied for the treatment of asthma [27–45].

4.2.6. Interleukin 33

IL-33 origin and actions are very similar to IL-25. Its effect is even greater and more potent on innate lymphoid cells compared to IL-25. In addition, it activates mast cells and basophils and is a survival factor for eosinophils [26].

4.2.7. Tumoral necrosis factor (TNF-a)

It is produced by epithelial cells, Th1 and Th17 cells. TNF-a promotes the recruitment of eosinophils and neutrophils to the airway by dysregulation of adhesion molecules. It activates macrophages for the production of growth factors and GM-CSF [25].

4.2.8. Intervention in the Th2 pathway with monoclonal antibodies

The possible therapeutic interventions with monoclonal antibodies for the treatment of asthma are outlined in **Figure 4**. The characteristics of the main molecules and the current evidence available for each of them are detailed in **Table 1** [27–45]. Other monoclonal antibodies have fewer studies and possibly have a residual role in the treatment of asthma [46–50].

5. Conclusion(s)

A significant percentage of patients with severe asthma do not achieve control of the disease despite receiving adequate treatment. Current guidelines are outdated and will be even more

if biomarkers and specific molecular susceptible of an intervention are not included in future guideline versions.

For now, omalizumab, the only biological treatment available for the management of severe asthma, continues influencing future studies aiming to evaluate new molecules and possible newer targets in selected patients. Linking the characteristics of each patient's disease, with the effects of a specific monoclonal antibody, will surely imply a much more effective and timely control of the disease.

The detailed approach of the phenotypic characteristics and their molecular basis should lead to a personalized treatment of great precision and effectiveness. A very promising new era in the treatment of asthma is approaching.

Conflict of interest

The authors declare no conflict of interest.

Author details

Dolly V. Rojas*, Diana L. Silva and Carlos D. Serrano

*Address all correspondence to: dollyvanessa@gmail.com

Allergy Unit, Fundación Valle del Lili, Faculty of Health Sciences, ICESI University, Cali, Colombia

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Chapter 10

The Asthma Obese Phenotype

Marina Ruxandra Oțelea and Agripina Rașcu

Additional information is available at the end of the chapter

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Abstract

Asthma is a very heterogeneous disease, with two major asthma phenotypes, the allergic and the late onset asthma, differentiated by the triggers, the cellular dominance, the Th1/Th2 inflammation pattern and the local and serological markers. As there were many overlapping biological markers between these two phenotypes, different types of tentative classification followed. A clinical one makes a difference between the predominant eosinophilic one (with better response to glucocorticoid) and the predominant neutrophilic one with more severe evolution and low rate of therapeutical improvement. Another approach was based on cluster analysis of asthma characteristics (onset, atopic status, and body mass index (BMI)), sensitivity to methacholine test, peak flow variability, bronchodilatation response, postbronchodilator level of FEV1, sputum eosinophil and neutrophil count, FeNO test, clinical symptom scores, treatment scheme to control symptoms, exacerbations, and severity. Emerging data suggest a distinct late onset obese-asthma phenotype, with a specific pathophysiology, comorbidities, and clinical evolution. This chapter reviews the main characteristics of this phenotype: the specific lung function impairment, the underlying inflammation, the adipokine profile, the comorbidities and the therapeutical approach. The mutual influence between obesity and asthma will be illustrated, whenever scientific data are available.

Keywords: asthma-obese phenotype, metabolic changes in asthma, inflammation in asthma, asthma biomarkers

1. Introduction

Obesity became in recent years a recurrence and one of the major concerns in asthma research. This chapter presents the relation between obesity and asthma, underlining the influences

on pathological mechanisms, evolution, and treatment, in order to give an overview of the current knowledge about the asthma-obese phenotype (AOP). Inside the AOP, two distinct forms have been described: an early onset, atopic asthma with no gender differences in incidence and a late onset, non-atopic asthma predominantly in women [1]. We interpret the first as an atopic asthma aggravated by obesity and the second as a form of asthma favored by obesity. They have common characteristics related to the pathological consequences of obesity, the subject of our review.

2. Incidence

Worldwide, 15–20% of the population suffers from asthma [2, 3]. The prevalence have different slopes in different countries, with higher incidence in developing countries [4] and apparently constant rate in recent years or even with a tendency of reduction in current wheezing in countries with previous higher prevalence [2].

The trends of incidence of asthma and obesity are similar: a flat curve of high prevalence in developed countries and an increasing prevalence in less developed countries [2, 5]. However, the recently published analysis from the US national survey, comparing the 8.5% population attributable fraction for overweight/obesity between 1988 and 1994 with the 11.9% one, in 2011–2014, found this increase statistically non-significant [6]. Studies from developing countries, in prospective cohorts, confirmed the parallel increase in incidence of obesity and asthma, [7], particularly in obese women [8].

The AOP could be, in fact, related not to obesity but to the metabolic syndrome. A Norway study confirmed, but another large longitudinal study with 25 years of follow-up contradicted this assumption and found that independent factors to the metabolic syndrome play significant roles in the association of asthma with obesity [9]. Waist circumference was negatively associated with eosinophilia [10] and gave an odds ratio (OR) = 1.46 for asthma in females [11]. The relation between asthma and metabolic syndrome seems to be reciprocal, as asthma increases the risk for metabolic syndrome [12] and for obesity [13].

High BMI is also associated with the severity of asthma, particularly in women [14], with a reduced FEV1 %, a higher readmission rate and longer hospitalization stay [15]. In a large cross-sectional Israeli study, obesity was associated with mild and moderate to severe asthma in male, and to moderate to severe asthma in females [16]. Differences in severity between obese and non-obese were maintained after adjustment for demographics, smoking status, medication or gastroesophageal reflux [17].

Genomic studies also support this association. A twin-based research concluded that 8% of the genetic component of the obesity is shared with asthma [18]. A large case control sample of population with European origin revealed a protection for asthma-obesity co-occurrence with the 16p11.2 inversion [19]. Several gene polymorphisms (TNF-α, -β or leptin receptors) with interrelated physiopathological mechanisms for the AOP seem to be involved in risk and/or the therapeutical response [20–23].

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3. Pathogenic pathways

Impressive research data have been accumulated to explain the relationship between obesity and asthma. Among them, two pathogenic processes draw special attention: the lung function impairment and the specific airways inflammation.

3.1. Lung function impairment

3.1.1. Structural changes

In normal obese, forced vital capacity (FVC) is smaller than slow vital capacity (SVC), and this points to the possibility of even underdiagnosis obstruction, when using FEV1/FVC data [24]. Reduced SVC and total lung capacity (TLC), increased inspiratory reserve volume, decreased expiratory reserve volume (ERV) and maximal voluntary ventilation volume (MVV) was found in severe obesity [25]. The reduction in FVC%, FEV1%, MVV% was parallel with the BMI increase [26]. The reduction in the functional residual capacity (FRC) was more pronounced than of the TLC until BMI exceeded 35 kg/m^2, after which the decrease was proportionate [27]. While VC and TLC are markers of restriction, the MVV integrates the endurance and strength of the respiratory muscles with the airway diameter and resistance and is interpreted as an obstructive dysfunction. Another argument against a pure restrictive pattern in obesity is that the FRC reduction is due to the ERV reduction, with normal or even increased RV and reflects a lower airways caliber [28]. The volume of FRC is the expression of the equilibrium between the inward elastic recoil of the lung and outward elastic recoil of the chest wall. Obesity, particularly the abdominal one, reduces the expansion of the diaphragm and of the excursions of the thoracic cage, limiting the elastic recoil of the lung. Ventilation occurs at lower lung volumes, the transpulmonary pressure is lower. These changes affect the retractive forces of the lung parenchyma and the airways caliber and unload the airway smooth muscle (ASM); as consequence, the ASM shortens more in response to external stimuli. Even more, due to the decreased expansion of the airways, actin and myosin attach closer and are more difficult to detach during relaxation. A confirmation of these mechanisms is obtaining no difference in the fall of FEV1 after methacholine test with or without a previous avoidance of deep inspiration in nonasthmatic obese (NAO) persons [29].

3.1.2. Metabolic changes

Obesity increases the respiratory demand, with greater energy expenditure for breathing. Obesity-related inflammatory cytokines (such as TNF-α or leptin) and hormones (insulin) increase the ASM contractility. The insulin growth factor 1 stimulates the proliferation of the ASM. Insulin raises the expression of β1-containing laminins, promoting contractility [30].

Successful weight loss programs reverse the lung function changes and have an important role in asthma management in these patients. Weight loss reduces airway resistance, airways obstruction, improves peak expiratory flow (PEF) variability, and increases FRC and ERV [31].

Weight loss in obese asthmatics (OA) with high IgE and dominant Th2 inflammation improved the resting respiratory system mechanics, assessed by oscillometry, but had no effect on the

sensitivity of air closure during the methacholine test, reflected by FVC % reduction. Certain differences in response, according to the underlying inflammation of the AOP subtypes, have been noticed [32] serving as argument that weight loss cumulates the benefit of the structural, the metabolic, and of the inflammatory improvement in OA.

3.2. Influences of the obesity inflammation pattern on asthma

Obesity generates a low-grade inflammation, switches blood monocytes and tissue macrophages to the M1 activation pathway, and impairs the ratio between regulatory T-lymphocytes (Treg) and Th17. Changes from the lean to obese pattern involve the switch of macrophages from M2 to M1 domination, switch from Th2 to Th1 cells, and switch from the Treg cells and NKT to B cells, mast cells and neutrophils. Together with the adipokine profile modification, a pro-inflammatory pattern develops (**Figure 1**).

3.2.1. Polarization of the macrophages

Macrophages are polarized to the M1 state by interferon-γ and by inducers of TNF-α, such as lipopolysaccharides (LPS). M1 macrophages upregulate pro-inflammatory cytokines as TNF-α, interleukin IL-1β, IL-6, IL-12, IL-15, and IL-23 and oxidative stress.

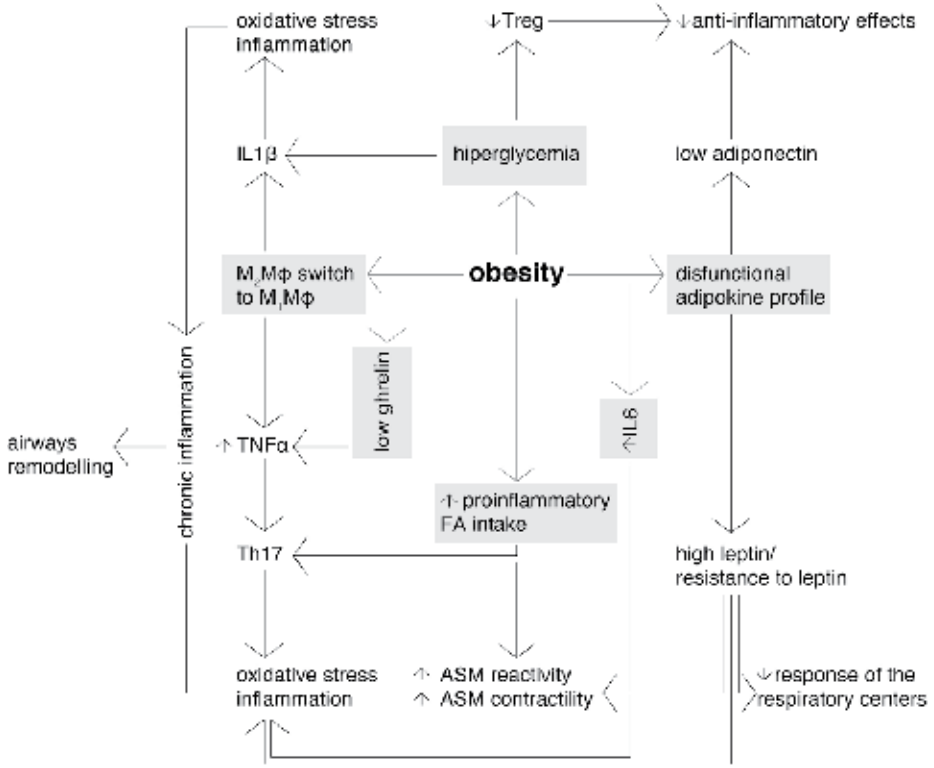

Figure 1. Obesity-related inflammation in asthma. ASM = airway smooth muscle; FA = fatty acids; IL1β = interleukin 1β, IL6 = interleukin 6; M1Mϕ = M1 macrophage; M2Mϕ = M2 macrophage; Th17 = T helper 17 cells; TNFα = tumor necrosis factor α; Treg = regulatory T cells.

Lung macrophages are a heterogeneous population divided into alveolar and interstitial macrophages. In non-allergic asthma, M1 macrophages are increased and pathogenic, while in allergic forms, they seem to be protective. Due to their defense capacity against pathogens, they have a role in preventing the asthma exacerbation. The most extensively investigated negative effects of the M1 polarization specific cytokine signature are TNF-α and IL-1β in asthma. Exogenous administration of recombinant TNF-α shifts to the left the curve of responsiveness to methacholine in normal subjects [33]. In asthma patients, high levels of TNF-α in bronchoalveolar lavage or bronchial biopsies are associated with severity [34]. How TNF-α induces airways hypersensitivity is not completely understood, but experimental research showed that TNF-α increases ASM contractility by intracellular calcium increase. The intimate process involves a variety of G-protein coupled agonists (methacholine, histamine and serotonine). After binding to TNF receptor 2, TNF-α increases the Th17 differentiation and induces vascular modifications through endothelin and neurotrophic tyrosine kinase receptor type 2. Of interest for obesity, a condition associated with low ghrelin levels is that the raise of TNF-α level in the bronchoalveolar lavage after ovalbumin challenge is attenuated by this orexigenic factor [35].

The IL-1β is a pro-inflammatory cytokine with special interest for bronchoconstriction, particularly if primed by IL-5. IL-1β is a result of activation of numerous lung cells, including lymphocytes, macrophages, mastocytes and even ASM. IL-1β could be the link between toll-like receptors (TLR) and nucleotide-binding oligomerization domain-like receptors (NLR), the NLRP3 inflammasome and the activation of the TH17 cells, as both TLR and NLR that sense the external signals promote IL-1β secretion [36]. From macrophages cytoplasm, IL-1 is secreted through lipid pores requiring the presence of gasdermin D (GSDMD), a protein identified from genomic-wide studies as a possible asthma marker [37]. Experimental data showed that GSDMD expression regulates cell growth of ASM and promotes fibrosis with remodeling of airways [38]. Cellular stress-related inflammation, with high extracellular release of adenosine triphosphate (ATP), uric acid crystals, and cholesterol also involve the IL-1β signal [39]. The expression of IL-1β is upregulated by prolonged hyperglycemic state [40], with possible impact on AOP.

3.2.2. The predominant Th1/Th17 activation

The level of Th17 increases in obese, if a certain threshold of the BMI is achieved, in absence of an acute or chronic inflammation [41]. An inhibition effect on adipogenesis in mesenchymal cells and on the adipocyte differentiation raised the hypothesis that IL-17 could be a regulatory cytokine of obesity itself, providing a negative feedback on the adipose tissue expansion [42]. Several mechanisms have been proposed to explain how Th17 increases in obesity. The higher metabolic activity related to nutrients intake raises the ATP level and the release of ATP molecules to the extracellular space; ATP binds to P2X7, a purinergic receptor, capable of driving Th17 responses during inflammation and secretion of pro-inflammatory cytokines [43]. Unhealthy diet, with high pro-inflammatory, long chain, saturated free fatty acid (FFA), and low anti-inflammatory ω3- polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFA) activates the TLR in adipocytes and macrophages, and the Th1/Th17 pathways in dendritic cells [44]. Micronutrient deficiencies, such as low levels of vitamin D, are also frequent in obese persons. The enhanced infection susceptibility is due to the decreased levels of cathelicidin in the primary defense cells, aggravating the clinical evolution.

In obesity, the adipocytes have a significant contribution to the circulating IL-6, promoting the differentiation of TH17 and naive CD4 T-cells. Leptin, another cytokine of the IL-6 family, is also increased, with many pathological implications for asthma. Among these, leptin modulates Th17 response by conditioning the signal transducer and activator of transcription 3 (STAT3) expression and phosphorylation in CD4 cells [45]. Th1 and Th17 differentiation require mammalian Target of Rapamycin 1 (mTORC1) signals [46], which are known to be activated by growth factors, amino acids or insulin, all being raised at obesity.

Through IL-17 secretion, Th17 cells recruit and activate neutrophils to produce pro-inflammatory cytokines (IL-6, IL-8) [41], chemokines, and adhesion molecules. IL-17 upregulates IL-8 secretion in airway epithelial cells and initiates airway remodeling, increasing the levels of fibroblast-derived inflammatory mediators, such as the α-chemokines, IL-8, and growth-related oncogene-α [41]. Pathogenic Th17 cells express IL-1R1, a type of IL-1β receptor, with bronchoconstriction effect [47].

Epigenetic markers, such as promoter methylation of transcription factors associated with increased Th1 differentiation, were found in OA preadolescent compared to non obese asthmatic patients (NOA) [48].

3.2.3. Reduction of Treg

Tregs have a significant role in suppression of allergy and asthma, as they are sources of anti-inflammatory cytokines (IL-10, TGFβ1 and IL-35) and have suppressor function on a variety of immune cells (B cells, NK cells, CD4+, CD8+) and dendritic cells. Tregs are even able to kill effector lymphocytes in a perforin-dependent manner. The number of studies related to the Treg number and function in asthma is increasing but are far from being conclusive: in allergic inflammation, Tregs are generally low and less able to control the inflammation process. An increased number of Tregs were found in more severe asthma, an effect that could be also due to the inhaled corticoids [49].

Concerning AOP, a reduction of Treg is present in insulin resistance OA [50]. Particularly with high amount of abdominal fat, Treg is reduced, contributing to the low-grade inflammation and insulin resistance development. Leptin has similar inhibitory effect on Treg [51]. Treg expresses the insulin receptor, and hyperinsulinemia affects their IL-10 production and the suppressor functionality [52]. As insulin levels are frequently elevated in obese subjects, the insulin effect on Treg could be a part of the explanation of the severity of asthma of the AOP.

3.2.4. The adipokine profile

The inflammation pattern in obesity is closely related to the adipokine profile. A meta-analysis of 13 studies with 3642 patients concluded that the high leptin and low adiponectin are associated with the diagnosis of asthma [53].

The leptin receptor is constitutively expressed in epithelial lung cells but also on immune cells. **Leptin** directly stimulates respiratory centers, increases frequency, minute and tidal volume. These positive effects on the respiratory function are lost in obesity, a state of leptin

resistance, but high dose of leptin administered to obese mice was able to restore the breathing pattern and the arterial CO_2 [54].

Compared to obese non-asthmatic, leptin levels are increased in OA [55]. The difference is higher in women [56] and in patients with lung neutrophilia [57]. High leptin level upregulates the expression of inflammatory proteins, such as cPLA2-α [58] or phospholipase D1 [59], raises leukotrienes (LT) production [60] and bronchial responsiveness. Again, the effect was manifest particularly in obese women [61]. LT synthesis in neutrophils depends on circulatory arachidonic acid, on nuclear localization of the 5-lipooxigenase [62], and on the level of extracellular signal regulated kinases (ERK) activity, significantly influenced by androgens. This might contribute to the gender differences in AOP.

Attenuation of the constitutive muscarinic activation of the ASM cells via the central nervous system (a normal dilatator effect and leptin) has been proposed as part of leptin resistance [63]. Leptin resistance seems to be selective, as the pro-inflammatory effects are maintained in obesity. Leptin effects on airway remodeling could be related to reduction in α1-antitripsin expression, enhanced intercellular adhesion molecule 1 (ICAM-1) expression and increase in the CCL11, G-CSF, VEGF, and IL-6 production [64].

The circadian secretion of leptin is the highest at midnight; in obese subjects, the basal and the evening increase is higher than in lean subjects [65]. This could be an influencer of the nocturnal asthma attacks and of the overall severity of asthma.

In contrast with leptin increase, plasma adiponectin is decreased in asthma [66], independent of the BMI [67]. The adiponectin is correlated with the FEV1 decline, and with the high serum and sputum IgE [68]. Adiponectin is able to polarize the macrophages to an M2 state [69], switches the balance by inhibition of pro-inflammatory cytokines (TNFα), stimulates the anti-inflammatory ones (IL10), diminishes Nf-Kb activation, and negatively correlates with protein C and IL6. Despite experimental data to confirm these actions, adiponectin's role in predicting asthma severity remains controversial.

Adiponectin circulates as trimer (the low molecular weight form) or hexamers (the high molecular weight form), and the inconsistent findings of these studies could be explained by different serum adiponectin components that were measured, as only high low-molecular-weight isoform was strongly associated with the asthma risk and lung function decrease [70].

4. Clinical and therapeutic particularities of OA

4.1. Biomarkers

The specific physiopathology of the AOP was translated in different attempts to define biomarkers. Particular biomarkers or different cut points for predicting airway inflammation were proposed. Classification and relevant examples of proposed biomarkers are summarized in **Table 1**. Most of these studies were not reproduced on larger scales, and currently there are no guidelines on their clinical utilization.

Category	Biological sample	Type	Comments
Inflammatory biomarkers	Sputum	High MMP1, MMP2, and MMP8	Study design primarily for asthma severity: these MMP not found in other clusters [71]
		IL-5	Comparison between OA and LA inside the group of severe asthma [72]
		14 differentially expressed genes encoding proteins related to the cell cycle and growth factor regulating pathways (MAPK1, E2F1, and SPRY2) and to the interferon signaling pathway (OASL, OAS3 and TRIM14)	Study design for cluster identification; the results selected refer to the comparison between late onset asthma, severe, high proportion of atopic, nonsmokers and obese female asthmatics, high frequency of exacerbations despite near normal lung function, 73.6% atopy. [73]
		Gene expression of calcium signal transmission (*S100P, S100A16),* lymphocyte differentiation (*MAL),* and mucin (*MUC1)* increase	Comparison of diet (high fat meal)-induced metabolism in asthma and healthy controls. No specific analysis related to BMI, but mean BMI was in the obesity range in asthma and in overweight range in controls [74]
	Exhaled breath condensate	Increase in glucose, n-valerate, acetoin, isovalerate, and 1,2-propanediol levels and a decrease in formate, ethanol, methanol, acetone, propionate, acetate, lactate, and saturated fatty acid levels	Relatively small cross-sectional study, well designed to differentiate AOP from obese-non asthma and lean-asthma, strong statistical power of correlation [75]
	Bronchial submucosa	Increased eosinophil count	In a severe asthma population, eosinophil number in submucosa correlated with BMI [72]
	Bronchial submucosa	No increase in eosinophil count	In mild to moderate OA, eosinophil number in submucosa not different from obese without asthma [76]
	Blood	Low periostin l	Study design primarily for asthma severity: low levels found also in other clusters, no difference between OAP and other cluster presented [71]
	Blood	CCL17, IL-4, IL-13	Cross-sectional study. Comparison of lean asthma and obese asthma [77]
	Expired air	FeNO test	Large cross-sectional study; low FeNO associated with adiposity indicators; in high FeNO group, adiposity indicators associated with worse asthma severity or control [78]
Adipokine profile	Blood	Leptin	Cross-sectional study, comparison to lean asthma AO, leptin mediates asthma control [77]

Category	Biological sample	Type	Comments
	Blood	Adiponectin	Review of the controversial epidemiological results in human studies mainly to heterogeneity of the design of these studies [79]
	Blood	Resistin	Post-weight management intervention Δ resistin negatively associated to Δ FRC and Δ RV [80]
Functional test (bronchial reactivity)		Challenge test with ozone	Comparison between obese and non-obese; post-exposure decrease of FVC in obese, similar bronchial reactivity and IL-6 increase [81]
		Challenge test with mannitol	Airway hyper-responsiveness to mannitol in obese non-asthmatic without asthma comparative to non-obese subjects [82]

Table 1. Asthma-obese phenotype biomarkers.

4.2. Comorbidities

The clinical manifestations and the treatment response appear to be influenced by comorbidities. They can be summarized as allergic (rhinitis, eczema), smoking-related, psychogenic (hyperventilation, depression, and anxiety disorders), metabolic syndrome, gastroesophageal reflux disease and obstructive sleep apnea [83]. Comorbidities become significant when there is reciprocal impact. As a disease is the expression of a certain number of dysregulated functional mechanisms, comorbidities, by cumulating more abnormalities, will always have a potential negative impact. Comorbidities might share co-determination factors or potentiate mechanisms for the related comorbidity. The asthma-obesity relation suits very well in these last categories.

In terms of co-determination factors, the chronic asthma inflammation is influenced by the metabolic inflammation, as previously described. Certain comorbidities, such as the gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA) have an independent high prevalence in asthma and in obesity but aggravate each other when they coexist.

4.2.1. Gastroesophageal reflux disease

To evaluate prevalence, different definitions of Gastroesophageal reflux disease (GERD) are used in the epidemiological studies: the presence of the reflux symptoms, the pH measurement, the endoscopic findings of the gastroesophageal mucosal disease or presence of the hiatal hernia. Despite the variation in methodology, the incidence was significantly higher than in the non-asthmatic population no matter what criteria were used. On the obesity side, a meta-analysis showed that the risk for GERD progressively increases with the increase in BMI

[84]. The asthma-GERD relation is bilateral. GERD is the cause for the abnormal acid reflux that leads to microaspiration into the airways, initiating reflex cough and bronchoconstriction via vago-vagal reflexes. Asthma bronchoconstriction triggers acid reflux, as happens in some patients during the methacholine test. Theophylline increases gastric acid secretion and lowers low esophagus sphincter tone [85]. Both obesity and asthma increase the transdiaphragmatic and intragastric pressures and favor hiatal hernia.

Despite common agreement that GERD was associated with more severe asthma symptoms, apparently, no association between GERD and the severity of asthma was found in a subpopulation of OA [86]. This emphasizes the need for dedicated studies to this particular phenotype.

Indirect arguments that asthma control might have positive influence on GERD are the presence of the silent reflux in asthma patients and the relative risk of development of GERD [87], but there are no published data to confirm this hypothesis.

GERD influences also obesity, by changing type and frequency of meals. Reduction in weight has favorable effects on GERD-related symptoms.

Due to the presence of the increased cholinergic tone in both asthma and GERD, the use of anticholinergic medication might be of interest.

4.2.2. Obstructive sleep apnea

Obstructive sleep apnea (OSA) has a higher prevalence in men, while OA is more prevalent in women. Due to the high association rate between OSA and asthma [86] and the worse asthma control in the presence of OSA, an overlap asthma-OSA syndrome was proposed [88]. As with the GERD, asthma increases the risk of the new-onset OSA [89]. Obesity is the major risk factor for OSA, but OSA also leads to obesity: impaired sleep architecture changes leptin signal with a reduction in satiety along with craving for high energy foods [90], modifies transcriptional networks in visceral fat, and reduces secretion of growth hormone. The excessive daytime sleepiness reduces physical activity, increases the proportion of the fat mass compared to the free fat mass and makes weight loss programs more difficult to succeed.

OSA has negative impact on asthma. During apnea episodes, the upper way vibration and suction collapse, activate vagal tone, and induce reflex bronchoconstriction. The more negative intrathoracic pressure developed during apnea increases the pulmonary capillary volume. These pathological processes trigger asthma attacks. Repeated mechanical trauma is associated with upper and lower airway inflammation [91]. OSA aggravates nocturnal asthma, lowers the quality of life, and leads to more frequent exacerbations.

Asthma has negative effects on OSA. In asthma patients, OSA is more severe, with lower apnea-hypopnea index (AHI). Sleep efficiency and arousal index were higher in severe asthma compared to moderate asthma, but apparently no correlation have been found between OSA severity and measures of the asthma severity evaluated by FEV1 or with the asthma quality of life score [92]. High dose, long-term corticosteroid treatment, particularly in poorly controlled asthma could be a contributing factor to obesity and OSA [93].

Nocturnal GERD links asthma, GERD, and OSA under a common aggravating factor. The increase of the respiratory effort exacerbates asthma and OSA symptoms and is associated with higher AHI and inflammation in the exhaled breath condensate [94].

4.2.3. Metabolic syndrome-related comorbidities

Increased incidence of type 2 diabetes and cardiovascular events (hypertension, ischemic heart disease, cerebrovascular disease) is also expected to happen, as directly influenced by obesity. In a very large adult study, elevated waist circumference and triglyceride (TG) and low high-density lipoprotein (HDL) were significantly associated with wheezing [95]. In this respect, statins represent a potential treatment modality in severe asthma; their anti-inflammatory effects and the enhancement of the corticosteroid sensitivity make them good candidates for AO treatment, particularly in cases with metabolic syndrome [96].

4.3. Therapeutical challenges

Current guidelines do not differentiate pharmacotherapy between OA and NOA, but studies have confirmed that AO is more severe and more difficult to control, with the regular medication [83, 97].

AOP benefits from **lifestyle** changes: weight reduction is a priority goal, but all other general asthma interventions should be addressed: smoking cessation, allergen exposure avoidance, occupational risk assessment, and so on. Diet and/or bariatric surgery is correlated with reduction of exacerbations and improvements in the lung function, clinical manifestations, and quality of life [98, 99]. Successful interventions increase in efficacy of the inhaled corticosteroids (ICS) after smoking cessation [100] and after losing weight [98].

Treatment of **comorbidities** related to overweight directly impacting asthma. Positive effects on asthma control have been reported from continuous positive airway pressure (CPAP) therapy of OSA [92]. There is also a benefit on the pulmonary function in OA with diabetes treated with dipeptydil-peptidase4 inhibitors related to the correction of the oxidative/antioxidative imbalances [101].

Proton pomp inhibitors and histamine H2 receptor improve GERD-related symptoms and quality of life but does not influence asthma control [102]. However, improvement of symptoms in severe, selected cases was obtained from different surgical procedures [103, 104]. However, the common high cholinergic tone in GERD and asthma raised the hypothesis that anticholinergic therapy could be a common solution [104]. A Cochrane systematic review provided some evidence that long-acting muscarinic antagonists added to ICS show some benefits on FEV1 [105], but prospective studies should confirm if there is also benefit in the AOP, and if this effect is higher in asthma-GERD association. The anti-inflammatory effect of statins in asthma is not consistent across studies [106]. Whether their effect on asthma evolution is increased in those OA with dyslipidemia remains to be demonstrated.

If standard step-increase asthma medication is not efficient, specific endotype treatment (precision medicine approach) would be desirable.

OA is associated with some specific inflammatory pathways activation, one of which is 5-lipoxygenase pathway inflammation; leukotriene antagonists have similar efficacy with ICS in the presence of obesity [107]. Some biological therapies for severe forms of asthma were proven beneficial also in OA. For example, in OA patients with raised eosinophils and high airways reversibility, Mepolizumab was more efficient in the reduction of exacerbations [108]. Nevertheless, the ones that targeted commonly upregulated pathways were not successful. For example, a 12 weeks treatment with Brodalumab (a human anti-IL-17 receptor) had no clinically meaningful effects [109]. Golimumab, an anti-THF-α humanized antibody, provided some improvements, but limited use due to the risks associated with this therapy: infections, congestive heart failure, malignancies, and demyelinating disorders [110]. However, in a small selected group of overweight and obese severe asthma patients this treatment reduced the oral steroid dose and hospitalizations [111].

5. Conclusions

To conclude, the AOP is supported by epidemiological, pathophysiological, and clinical data. There are still many uncertainties about the OAP and even more about the two subtypes, described until now only from the epidemiological perspective; further research is needed to elucidate common and specific mechanisms and to improve our knowledge about the specific biomarkers and the therapeutical approaches for the subtypes of AOP.

Author details

Marina Ruxandra Oțelea[1]* and Agripina Rașcu[1,2]

*Address all correspondence to: marina.otelea@umfcd.ro

1 University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

2 Colentina Clinical Hospital, Occupational Medicine Department, Bucharest, Romania

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Chapter 11

Use of Omalizumab as Treatment in Patients with Moderate and Severe Non-Atopic Asthma and Associated with Asthma-COPD Overlap Syndrome (ACOS)

Herrera García José Carlos,
Arellano Montellano Ek Ixel,
Jaramillo Arellano Luis Enrique,
Espinosa Arellano Andrea,
Martínez Flores Alejandra Guadalupe and
Caballero López Christopherson Gengyny

Additional information is available at the end of the chapter

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Abstract

The asthma syndrome has many manifestations, termed phenotypes that arise by specific cellular and molecular mechanisms termed endotypes. Understanding helps clinicians make rational therapeutic decisions. Omalizumab has been widely used in clinical practice in Europe and America for over a decade as an add-on therapy to treat patients who have severe asthma. These real-world clinical effectiveness studies have confirmed the benefits, cost-effectiveness, and clinical utility. The purpose of this review is to present the effects of anti-IgE treatment in severe non-atopic asthma and in asthma-COPD overlap syndrome (ACOS). This study describes that the use of omalizumab therapy reduces IgE expression and IgE sensitization of target cells within the bronchial mucosa while exerting a favorable effect on lung function in the short term, as assessed by changes in forced expiratory volume in 1 s (FEV1).

Keywords: omalizumab, non-atopic asthma, ACOS, phenotypes, severe asthma

1. Introduction

Severe asthma is a highly heterogeneous and burdensome disease that requires individualized assessment and management. The exact prevalence of severe asthma is unknown, but it has been reported to affect 5–10% of the population with asthma. Although some patients have

Atopic Patient	Non-Atopic Patient
With o without Eosinophilia	With or Without Eosinofilia
Skin prick test positive	Skin prick test negative
IgE > 150 U/L	IgE < 30 U/L
	30-150 U/L
	or > 150 U/L

Figure 1. Definitions.

asthma that remain poorly controlled despite high doses of inhaled corticosteroid (ICS) with or without additional controlled therapies including long-acting muscarinic antagonists and theophylline. Uncontrolled severe asthma significantly affects the activities of daily living, morbidity, mortality, quality of life (QOL), and health care use. Indeed, severe asthma accounts for approximately 50% of all asthma-related health care costs, direct (physician visits, hospitalizations, intensive care, and medications) and indirect (missed school days and work absenteeism). Categorically, uncontrolled and severe asthma remains a health and economic burden in many countries. Nowadays, we have a targeted therapy to control the burden disease with excellent results. In this chapter, we discuss the benefits of the use of omalizumab (OmAb) in patients with non-atopic and asthma COPD overlap syndrome (ACOS) phenotype. [1] (**Figure 1**).

2. Non-atopic asthma and IgE

The concept of asthma in our practice is a complex disease. Atopy is a familiar knowledge but the significance of non-atopic or non-allergic is a new definition to treat the patients with moderate-to-severe asthma. The presence of negative prick test and presence or not of eosinophilia is an opportunity to use biologics to improve symptoms and quality of life [2–3]. The possible association of serum IgE levels with asthma, irrespective of specific allergic sensitization has long been investigated. Burrows et al. revealed that IgE-mediated mechanisms might play a role even in non-atopic asthmatics with no detectable allergen-specific IgE. Some studies have shown that up to 25% of adult asthmatics are non-allergic. We proposed to treat the patients according to different types [4–6] (**Figure 1**).

A minority of asthmatic individuals are not however demonstrably atopic by conventional criteria, which has led to the suggestion that asthma maybe divided clinically into atopic and non-atopic. Recently, there have been major advances in our understanding of the molecular mechanisms of non-atopic. Indeed, the mechanisms of this variant of asthma in which allergens have no obvious role in driving inflammatory process in the airways remain uncertain. This type of research will certainly point towards new types of mechanisms, which will allow a more personalized way to treat asthma [7].

3. Local and peripheral IgE synthesis in severe asthma

Non-atopic asthma patients are typically a late-onset condition, more common in females, and it tends to be more severe than atopic form, requiring higher doses of corticosteroids for

Cell types of epithelial components	Atopic asthma	Non-atopic asthma
Ciliated columnar	Damage ++	Damage +
Desmosomes	Breakdown ++	Breakdown +
Globlet cells	Hyperplasia (+)	Hyperplasia (−)
Basal cells	Damage +	Damage +
Basement membrane	Thickening ++	Thickening +
Eosinophils	Infiltration +++	Inflitration +++
Neutrophils	Inflitration +	Inflitration ++
Mast cells	Inflitration ++	Infiltration +
Lymphocytes	Infiltration +++	Infiltration ++
Macrophages	Infiltration +	Infiltration ++

Table 1. Comparison of bronchial epithelial components in atopic and non-atopic asthma.

adequate control. It often starts following a severe upper or lower respiratory tract infection or during pregnancy, but it also indicates that environmental factors may be more important in the causation of non-atopic asthma. The presence of increased local synthesis of IgE also in non-atopic asthmatics has been demonstrated in more recent studies. Ying et al. showed local expression of epsilon heavy chain of IgE in the bronchial mucosa in atopic and non-atopic asthmatics. Mouthuy et al. confirmed that local IgE production occurs in the bronchial mucosa in atopic asthma and showed for the first time, that this part of IgE is directed towards house dust mite allergens. [8–10].

We described in 2015, the presence of non-atopic phenotype in a population of 10 asthmatics in a cohort with omalizumab treatment in University Hospital of Puebla, Mexico. Since the identification of IgE as a major stimulus in the inflammation cascade, the development of agents to target IgE has thrived. [11] (**Table 1**).

4. Anti-IgE drug omalizumab: mechanism of action

Omalizumab (OmAb) is a recombinant humanized monoclonal antibody that was designed to bind to IgE on the Fc (constant fragment) portion, C epsilon 3 locus, in the same domain where IgE is bound to FcRI. This drug was synthesized with the aim of sequestering free IgE and reducing allergic inflammation. This drug is administered subcutaneously and is absorbed slowly. The peak of serum concentration is reached after 7–8 days and it is eliminated via reticuloendothelial system having a half-life of around 26 days. It has been accepted for a long time that OmAb acts on the free IgE and abolish the binding of IgE to FcRI or FcRII, CD23 cells, B-cells, dendritic cells (DC), eosinophils (Eo), and monocytes. In several real-life studies, the use of OmAb has been associated with an absence of exacerbations and improvement in the quality of life, which is reflected in reduced hospital admissions and emergency visits but not in pulmonary function. The standard duration of treatment with OmAb has not been established to date. A follow-up study showed that after 6 years of OmAb treatment,

most patients have mild and stable asthma in the ensuing 3 years after treatment discontinuation, it has been suggested that the persistence of the effects of OmAb may be due to its ability to curtail airway remodeling in patients with asthma. In fact, it has been found that OmAb significantly decreased the airway wall area. After 1 year of omalizumab treatment, a significant mean reduction in eosinophilic infiltration was recorded as well as a reduction in the reticular base membrane in bronchial biopsies from patients with severe persistent allergic asthma was observed. These findings indicate that OmAb may modify the course of the disease due to their possible influence curtailing airway remodeling [12].

5. Anti-Immunoglobulin E in non-atopic asthma with omalizumab

In an attempt to elucidate the drug's mechanism of action, OmAb regulated FcRI expression negatively on basophils and plasmacytoid dendritic cells and increased forced expiratory volume in the first minute (FEV1) compared with baseline after 16 weeks in patients with severe non-atopic asthma demonstrated the possible role of IgE in non-atopic asthmatics [12–14]. The concept of Omalizumab treatment in non-atopic asthma is a new provocative idea and initially, some reports cases and data from severe asthma registries gave food for thought and discussion [15–16].

We concluded the functional role of local polyclonal IgE in airway mucosal tissue also in view of the finding of eosinophilic inflammation in nasal polyps with increased local tissue IgE levels independently of the allergic status of the patients. We presented the same case to Mexican female patient in University hospital of Puebla and showed the benefits of omalizumab in symptoms, QOL, and acute exacerbations, not in pulmonary function [13, 17].

6. Effects of omalizumab in non-atopic asthma patients

Eosinophilic asthma has been considered a phenotype of severe asthma. Allergic asthma can present with normal or increased numbers of eosinophils. The guidelines generally do not distinguish between the pathways responsible for the eosinophilia (atopic or non-atopic). Omalizumab can decrease the number of eosinophils in sputum on the bronchial mucosa and to a lesser extent in peripheral blood, in some cases, omalizumab fails to improve allergic asthma, this in probably due to the fact that the predominant physiopathological dysregulation comer initially from adaptive immunity, probably as a consequence of the highly intense activity of the allergic cascade. [18–19].

As a result of all these different modes of action, omalizumab has also been shown to interfere in certain stages of the remodeling process. [20–23]. Kutlu et al. described a case with 34 years old male patient the use of omalizumab with negative skin prick test and IgE in 203 U/L, they use omalizumab a dose of 225 mg every 2 weeks and after 6 months the patient was scored as 7 to 25 points at the asthma control test before the treatment of anti-IgE. We described and showed the improvement or non-atopic patients with omalizumab and started with 150 mg of omalizumab in our asthma Clinic in Puebla and increased the doses with excellent results [20–24].

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7. Asthma-COPD overlap syndrome

Asthma and chronic obstructive pulmonary disease (COPD) are two common respiratory disorders which are associated with chronic inflammation or the airways. In text books, the two are described as distinct disorders, however, there is increasing awareness that in clinical practice many patients may have features of both. ACOS is a subset of patients with persistent airflow limitation who have clinical features of both asthma and COPD. (25).

Patients with ACOS have largely excluded from studies and hence information on their epidemiology, pathogenesis and treatment is sparse, we described in a COPD cohort from pneumology department in our asthma COPD clinic prevalence was 10 and 25% in asthma cohort. Another study described in COPD cohort has 15% of them fulfilling criteria for ACOS. Another study done in asthmatics who were smokers, found that 27% of them had ACOS. However, another study done showed that only 7% of asthma/COPD patients had ACOS. This wide variation can be partly attributed to the difference in the criteria used to diagnose ACOS in the above studies. The lack of consensus on a definition for ACOS has led to the wide range in prevalence varying between 11 and 56% among COPD, 13 and 61% among asthma, and 2% among the general population [25–30] (**Tables 2** and **3**).

Major criteria	Minor criteria
1. Persistent airflow limitation (post bronchodilator FEV1/FVC ratio < 0.70 of lower limit of normal) in individuals aged 40 years or older.	1. Documented history of atopy or allergic rhinitis.
2. At least 10 pack years of tobacco smoking or equivalent exposure to indoor of outdoor pollutants (biomass).	2. Bronchodilator response (BDR) using 400 mcg of albuterol/salbutamol >200 ml and 12% from baseline values on 2 or more visits.
3. Documented history of asthma before the age of 40 years or BDR >400 ml in forced expiratory volume in 1 s (FEV1).	3. Peripheral blood eosinophil count >300 cells/μL.
FVC = Forced vital capacity	
The criteria for diagnosis of ACOS consist of 3 major and 3 minor criteria. To diagnose ACOS, it is necessary to have 3 major criteria and at least 1 minor criteria.	

Table 2. Expert consensus major and minor criteria for ACOS.

Major criteria	Minor criteria
1. Very positive bronchodilator test (increase in FEV1 > 15% and >400 ml	1. High Level of total IgE
2. Sputum eosinophils	2. Personal history of atopy
3. History of asthma	3. Positive bronchodilator test on at least 2 occasions (increase of FEV1 > 12% and 200 ml).
For diagnosis at least 2 major criteria of 1 major criteria with 2 minor criteria.	

Table 3. SEPAR criteria for mixed COPD/asthma phenotype in COPD.

8. Recently use of biologicals for ACOS

In the past decade, interest in the clinical characteristics, importance and consequences for patients with overlapping features of asthma and COPD has been renewed. In their purest forms, asthma and COPD are distinct and readily recognizable clinical entities. Furthermore, guidelines for treatment of asthma and COPD are well established and evidence-based.

The unknowns continue to mount for patients in this overlap syndrome group who are unresponsive to existing treatments but continue to be symptomatic and at increased risk for exacerbations. The absence of treatment guidelines becomes particularly problematic when the use of biological is being considered. Experience with biological is most extensive with asthma, but studies of asthma treatments often exclude subjects with a history of smoking. Furthermore, in studies in COPD, a history of asthma is usually and exclusion criterion. Therefore, well recognized evidence-based guidance is largely absent as to what might be the best therapeutic approach, what patient characteristics are most predictive in selecting a specific next treatment of what outcomes are most likely to reflect treatment responsiveness. As many patients with asthma-COPD overlap syndrome might not achieve disease control with existing treatments, the consideration for and selection of a biological agent is an important unmet clinical need, both for the clinician and the affected patient [31].

Chest, Steven Maltby and colleagues at the University of Newcastle in Australia began to address this largely open question. What are the effects of omalizumab in this patient cohort? The Australian Xolair Registry was used to evaluate the real world use of omalizumab for severe uncontrolled allergic asthma. A total of 177 participants were evaluated and 17 of these had a doctor diagnosis of COPD. Omalizumab was found to be equivalently effective in patients with severe allergic asthma and a physician diagnosis of COPD, as well as severe asthma without COPD. In severe asthma and COPD, the asthma control questionnaire (ACQ) improved from 3.68 to 1.69 with the addition of omalizumab [31].

Initial studies have shown that omalizumab may be useful in patients with ACOS. It has been shown to improve symptoms, reduce exacerbations and hospitalization, and improve lung function parameters and reduced steroid requirement in these patients. However, larger randomized trial is required to further validate this observation. We presented the effects of omalizumab in ACOS patients with an excellent result in a group of 5 patients of the asthma COPD cohort clinic in University hospital of Puebla and showed improved lung function and symptoms [31–33].

Nayci et al. published the effectiveness of omalizumab treatment in asthma-COPD overlap syndrome in 2016 and described a clinical reduction in exacerbations and steroid requirement and improved symptoms and pulmonary function parameters in 6 patients. Dammert et al. published the use of Omalizumab in patients with COPD and atopic phenotypes in 7 cohort patients with positive allergy test and showed that omalizumab reduced the number of exacerbations, hospitalizations, and improved symptoms [34–35].

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9. Conclusion

To conclude, there is now evidence suggesting that omalizumab improves patients with severe non-atopic asthma and ACOS. Therefore, it is important to review each patient meticulously and regularly and provide personalized and targeted treatment. In the case of using omalizumab to treat non atopic severe asthma, the evidence is conclusive in these phenotypes. In the era of personalized and targeted medicine, it is important to fully characterize our patients and prescribe treatment that aims at treating the particular patient to consider the cost-effectiveness. In this chapter, we described that omalizumab is efficient and safe to treat and improves and increases the quality of life.

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Conflict of interest

None.

Author details

Herrera García José Carlos[1]*, Arellano Montellano Ek Ixel[1], Jaramillo Arellano Luis Enrique[3], Espinosa Arellano Andrea[3], Martínez Flores Alejandra Guadalupe[1] and Caballero López Christopherson Gengyny[2]

*Address all correspondence to: jchg10@yahoo.com.mx

1 Asthma-COPD Clinic-University Hospital of Puebla, Mexico

2 University Hospital of Puebla, Mexico

3 Benemerita Autonomous University of Puebla, Mexico

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Chapter 12

Cough Variant Asthma as a Phenotype of Classic Asthma

Sanela Domuz Vujnović, Adrijana Domuz and Slobodanka Petrović

Additional information is available at the end of the chapter

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Abstract

Cough variant asthma (CVA) was first described by Glauser. CVA was described as the isolated chronic cough as the only presenting symptom responsive to bronchodilator therapy. The authors now suggest that CVA is present with airway hyperresponsiveness, eosinophilic inflammation of central and peripheral airways and bronchodilator responsive coughing without typical manifestation of asthma such as wheezing or dyspnea. Pathologically, CVA shares common features such as eosinophilic inflammation and remodeling changes with classic asthma. Because of that, CVA is clinically considered as a variant type of asthma, a phase at the beginning of asthma pathogenesis or as a precursor of classic asthma. Nearly 30% of patients with CVA eventually develop intermittent wheezing, an average of 3–5 years. It is clinically very important to recognize CVA because long-term inhaled corticosteroids can significantly decrease the development of classic asthma in these patients.

Keywords: asthma, cough variant asthma, airway hyperresponsiveness, chronic cough, airway remodeling, airway inflammation

1. Introduction

Asthma could be defined more as a syndrome characterized by several different phenotypes [1–3]. Therefore, one of the possible definitions describing the characteristics of the disease and unifying more different definitions could define asthma as chronic inflammatory disease characterized by acute variable onset of symptoms (coughing, air deficiency, chest tightening) with bronchoconstriction (clinical definition) reversible and passes spontaneously or under

the impact of therapy (pharmacological definition), followed by bronchial hyperactivity on different stimulants (functional definition) and the inflammation of different stage, duration and difficulty (biological definition) [1]. Cough variant asthma (CVA) is defined as a phenotype of asthma, which characterized by cough as the sole symptom and airway hyperreactivity (AHR) [4]. Corrao and colleagues first defined "cough variant asthma" as AHR, chronic cough and absence of wheezing [5].

The authors agree that CVA and classic asthma have the same pathophysiological and immunological mechanisms, so CVA is considered a precursor of classic asthma [6–8].

Case 1 [9]: A 5-year-old boy presented to the clinic because of prolonged dry coughing with no history of wheezing. Because boy could not do spirometry, a forced oscillation technique was made. The total respiratory resistance was decreased by −20.4% after beta-2-agonist inhalation. At the first visit, 2-week therapy of inhaled beta-2-agonist was started. This treatment was clearly effective against his cough. The CVA was diagnosed, and his treatment with leukotriene receptor antagonist (Montelukast) and LABA (tulobuterol patch) was started for next 8 weeks. Eight months later, boy has the same symptoms. The same treatment was restarting. Three years later, boy has another episode of a dry cough with no complaints of wheezing. A physician confirmed a wheeze during expiration by auscultation. The treatment with inhaled steroid (Fluticasone), LABA (Salmeterol) and leukotriene receptor antagonist (Montelukast) was started. Over time, after boy developed recurrent wheezing, the diagnosis of asthma was set.

Case 2 [10]: "A 64-year-old female presented to the clinic as a self-referral complaining of a persistent cough." She said that the symptoms last for almost 17 years. The patient had diagnosed seasonal rhinosinusitis with positive skin prick test. Previous evaluations were all unremarkable. She underwent a methacholine challenge test. Spirometry showed increase in FEV1 with a 13% change from baseline. The patient was diagnosed with CVA and therapy with a combination of medium dose inhaled steroid and long-acting beta-2-agonist (Mometasone/Formoterol) was started.

Case 3 [11]: "A 32-year-old women presented with an intermittent nonproductive hacking cough that had lasted several days." Her medical history was unremarkable, and previous evaluations were normal. Results of a methacholine challenge test showed severe airway hyperreactivity. The patient was diagnosed with CVA, and bronchodilator with ICS treatment was started.

The prevalence of CVA is unknown, and from these cases it can be noticed that patients with chronic cough, as the only symptom, remain unrecognized as asthma for a long-time period.

The isolated cough is less common than other clinical manifestations of classic asthma [11]. Diagnosis of CVA may prove to be a challenge for the physicians. Therefore, evaluation results of patients with CVA are usually normal (spirometry, skin prick test, chest radiography, blood test) [12]. Previous clinical history is also normal in these patients [2, 11, 13].

Clinical feature of CVA is a good response to bronchodilator and ICS therapy [12, 13]. Studies have shown that the ICS therapy in CVA patients prevents the development of classic asthma [3, 7, 12]. Namely, it has been noticed that an average of 30% of patients with CVA without treatment

develop classic asthma with wheezing [3]. A smaller number, about 10% of patients with CVA and with adequate therapy (bronchodilator, ICS or Montelukast) develop classic asthma. A good response of chronic cough to the therapy with ICS cannot be used to distinguish other cough present diseases (atopic cough, non-asthmatic eosinophilic bronchitis) from CVA [2, 8].

It should be emphasized that in patients with chronic cough, a diagnostic evaluation for asthma should be performed.

2. Pathological mechanism underlying CVA

The main underlying pathophysiological mechanism of CVA is airway hyperresponsiveness (AHR) [3]. Airway hyperresponsiveness in CVA patients is milder than in patients with classic asthma. AHR is defined by two basic parameters: bronchial sensitivity and bronchial reactivity.

Airway remodeling is milder in CVA than in classic asthma [14, 15]. The more important is their airway sensitivity (threshold dose of methacholine to increase respiratory resistance) and airway reactivity (slope of respiratory resistance response curves), which are tested by challenge tests [15]. The difference in the challenge test between CVA and classic asthma patients was only in airway reactivity. Since bronchial reactivity is the one that is crucial in patients with CVA, there is a normal baseline result in these patients, but only challenge tests are positive [15, 16]. Airway reactivity is lower in CVA patients mostly because bronchoconstriction is lower and limited in CVA. Niimi et al. suggested that airway remodeling does not protect against bronchial sensitivity but against bronchial reactivity [15]. Bronchial hyperreactivity plays a significant role in the pathophysiology of CVA development. Cough reflex sensitivity does not change in patients with CVA, and it is not essential in pathophysiology in CVA [7, 8].

An important role in the pathophysiology of CVA has eosinophilic inflammation [3]. The results of studies have shown that BAL and sputum in patients with CVA contain an increased percentage of eosinophils [2]. Also, the studies showed that there was no significant difference between CVA and classic asthma in the sputum levels of eosinophilic cationic protein, interleukin 8 (IL-8) and levels of exhaled nitric oxide (FeNO) [2, 7, 12, 17, 18]. Studies have suggested that the basic pathophysiological characteristics of CVA are eosinophilic inflammation and AHR [3].

Bronchoconstriction is milder in CVA than in classic asthma patients, and this can be a possible reason why these patients do not have wheezing as a symptom [16]. The main puzzle in the clinical feature of CVA is the absence of wheezing. One of the possible mechanisms may be slower and limited bronchoconstriction. The possible cause of this slower bronchoconstriction may be airway remodeling [12] and variations in cytokine production [16].

The bronchodilatory test in patients with CVA is often negative because baseline FEV1 values are normal in CVA patients [12]. Corrao and colleagues defined “cough variant asthma” as AHR, chronic cough and absence of wheezing [5]. The peak expiratory flow (PEF) assessment does not show any variability in CVA patients [2]. The spirometric measurements are normal in patients with CVA [2].

Structural changes such as subepithelial thickening, goblet cell hyperplasia and vascular proliferation in the bronchial tree were noticed in patients with CVA [12]. These changes are less expressed than in patients with classic asthma and most commonly associated with airway inflammation. An important role in the development of cough in CVA patients has inflammatory mediators such as histamine, prostaglandins D2 and E2, leukotrienes C4, D4 and E4 [12, 19]. The study by Liu et al. showed similarities between AHR and the level of inflammatory biomarkers (IL-5, IL-10 and eosinophils in induced sputum) [3].

Because of this, researchers agree that early anti-inflammatory treatment in patients with CVA can prevent the development of classical asthma in these patients [7, 15].

The pathophysiological aspects of CVA are similar to classical asthma [7, 16]. The study of Fujimura et al. also showed that the use of ICS prevents the development of classical asthma in patients with CVA [7].

It is necessary to emphasize that further investigations in this matter are necessary.

3. Biomarkers and diagnostic criteria

Patients with CVA frequently report that cough is provoked by trivial stimuli (cold air, talking, etc.) and do not respond to the antitussive preparations [3].

Mochizuki and associates in their study showed that children with CVA have slower bronchoconstriction against non-specific airway stimuli, but have significant bronchial sensitivity as well as children with classical asthma [16]. Children with CVA show latent bronchoconstriction without wheezing [16].

Bronchodilatatory test, spirometry and chest radiography are usually normal in patients with CVA. The bronchodilatory test in patients with CVA is often negative because baseline FEV1 values are normal in CVA patients [12]. Methacholine testing has a positive predictive value up to 90, a negative predictive value of 100 for CVA [11, 20].

The more important is their airway sensitivity (threshold dose of methacholine to increase respiratory resistance) and airway reactivity (slope of respiratory resistance response curves), which are tested by challenge tests [15]. The difference in the challenge test between CVA and classic asthma patients was only in airway reactivity. Airway reactivity is lower in CVA patients mostly because bronchoconstriction is lower and limited in CVA [12].

Positive challenge test and good response on bronchodilator or ICS therapy can be criteria for diagnosis of CVA [11]. Improvement of chronic cough with bronchodilators is the essential diagnostic feature of CVA [12, 13, 21].

The study by Liu and et al. showed similarities between AHR and the level of inflammatory biomarkers (IL-5, IL-10 and eosinophils in induced sputum) [3]. The improvement of these criteria was lower in the classic asthma group with the ICS therapy. The IL-5 level in the CVA group decreased after 3 months of treatment, while in the classic asthma group decreased after 6 months of treatment. The percentage of eosinophils in the sputum decreased after 6 months of ICS treatment in the CVA group and after 12 months in the classic asthma group.

Biomarkers that can be used in diagnosis of CVA do not differ from biomarkers in classic asthma. Studies have shown that there are elevated sputum markers (eosinophils, IL-5, IL-10, prostaglandins D2 and E2, leukotrienes C4, D4 and E4) in patients with CVA [12]. Patients with CVA have structural changes in the bronchial epithelium such as subepithelial thickening, goblet cell hyperplasia and vascular proliferation [12]. These changes are less expressed than in patients with classic asthma.

Fractional exhaled nitric oxide (FeNO) is a biomarker that is related to allergic cough [1]. FeNo levels were significantly higher in patients with CVA or classic asthma than in healthy controls in the study by Shimoda et al. [22]. Patients with CVA have significantly lower FeNO than patients with classic asthma. In this study, FeNO values correlated with the severity of asthma symptoms [22]. Asano et al. had the same results in their study [23].

Another significant marker that is listed in the literature as a useful marker of inflammation in classic asthma is serum high sensitivity C-reactive protein (hs-CRP). Serum hs-CRP levels were significantly higher in patients with CVA and classic asthma. However, no significant difference was detected between CVA and classic asthma patients. Studies have shown that the levels of FeNO rise in patients with CVA and classic asthma. Serum hs-CRP is considered inappropriate as a marker of airway inflammation. Namely, this marker is higher in men than in women, also its values are elevated in other various systemic inflammations, arterial hypertension, diabetes and cardiovascular disease. The values of hsCRP are also elevated in smokers [22].

The authors of CVA studies agree that the criteria proposed by the Japanese Cough Research Society are adequate for diagnosing CVA [6, 8, 13]. The above criteria are as follows [13]:

- isolated chronic non-productive cough lasting more than 8 weeks;
- absence of a history of wheeze or dyspnea, and no adventitious lung sounds on physical examination;
- absence of postnasal drip to account for the cough;
- FEV1, FVC, and FEV1/FVC ratio within normal limits;
- presence of bronchial hyperresponsiveness (PC20 < 10 mg/mL);
- cough reflex sensitivity within normal limits (C5 > 3.9 mmol/L);
- no abnormal findings indicative of cough etiology on chest radiograph and
- relief of cough with bronchodilator therapy.

If all the criteria are fulfilled, a diagnosis of CVA can be made. However, if some of the criteria are not presented, the diagnosis of CVA can be set if the following criteria are fulfilled [13]:

- cough without wheezing lasting 8 weeks or more and no wheezing on auscultation
- no upper respiratory tract infection and
- relief of cough with bronchodilator therapy.

The most important criterion is the response to bronchodilator therapy that can be excellent when cough was totally resolved, good when sleep and daytime quality of life were improved, fairly good when severity and frequency of cough were somewhat decreased and poor when cough was unchanged [6].

4. Therapy

Therapeutic approach for CVA is similar to the treatment for classic asthma [10, 12]. Therapy with short-acting bronchodilators can be useful in patients with intermittent cough. Most of researchers agree that eosinophilic inflammation and remodeling require ICS therapy especially in patients with persistent cough [12].

The choice of ICS, its dose and duration of therapy should be as in patients with classic asthma. The results of the studies show that early application of ICS therapy reduces the risk of progression of CVA to classical asthma [8, 12, 21]. Namely, an average of 30% of patients with CVA without treatment develop classic asthma with wheezing in the future [3, 7]. A smaller number, about 10% of patients with CVA and adequate therapy (bronchodilator, ICS or Montelukast) develop classic asthma [12].

The study by Liu and et al. showed similarities between AHR and the level of inflammatory biomarkers (IL-5, IL-10 and eosinophils in induced sputum). The IL-5 level in the CVA group decreased after 3 months of ICS treatment, while in the classic asthma group decreased after 6 months of treatment. The percentage of eosinophils in the sputum decreased after 6 months of ICS treatment in the CVA group and after 12 months in the classic asthma group [3].

A fact that significantly influences the therapeutic response in children is described by Hutton et al. The fact is that "the parents who wanted medicine at the initial visit reported more improvement at follow-up regardless of whether the child received a drug, placebo or no treatment" [24, 25].

5. Differentiation of the reactive airway diseases

Whether CVA represents a self-standing airway disease is still the object of debate. CVA is pathophysiologically similar to asthma, but with mild bronchial hyperreaction and eosinophilic inflammation [6, 7]. CVA has been considered a precursor of classic asthma [6, 7].

Reaction to bronchodilator therapy could be a pathognomic feature in the differential diagnosis of CVA [7]. Namely, in conditions such as postnasal drip induced cough, gastroesophageal reflux associated cough and atopic cough bronchodilators have no antitussive effect [7, 26].

The presence of eosinophilia in the sputum, bronchial hyperactivity and a positive bronchodilator test is a sign of a stronger immune response of the respiratory tract. In essence, the differences between CVA and classical asthma are in the immune system's response to different stimuli [27].

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6. Evaluation of chronic cough in children

A cough is a natural and universal occurrence, and it is a part of the body's defense mechanism of the respiratory system. Chronic cough is defined as lasting more than 4 weeks in children and more than 8 weeks for adults [26, 28–30]. Diagnosis and management of patients with chronic cough are challenging for clinicians. Chronic cough can be a primary symptom of a variety of underlying conditions [25, 31]. The most common conditions that cause chronic

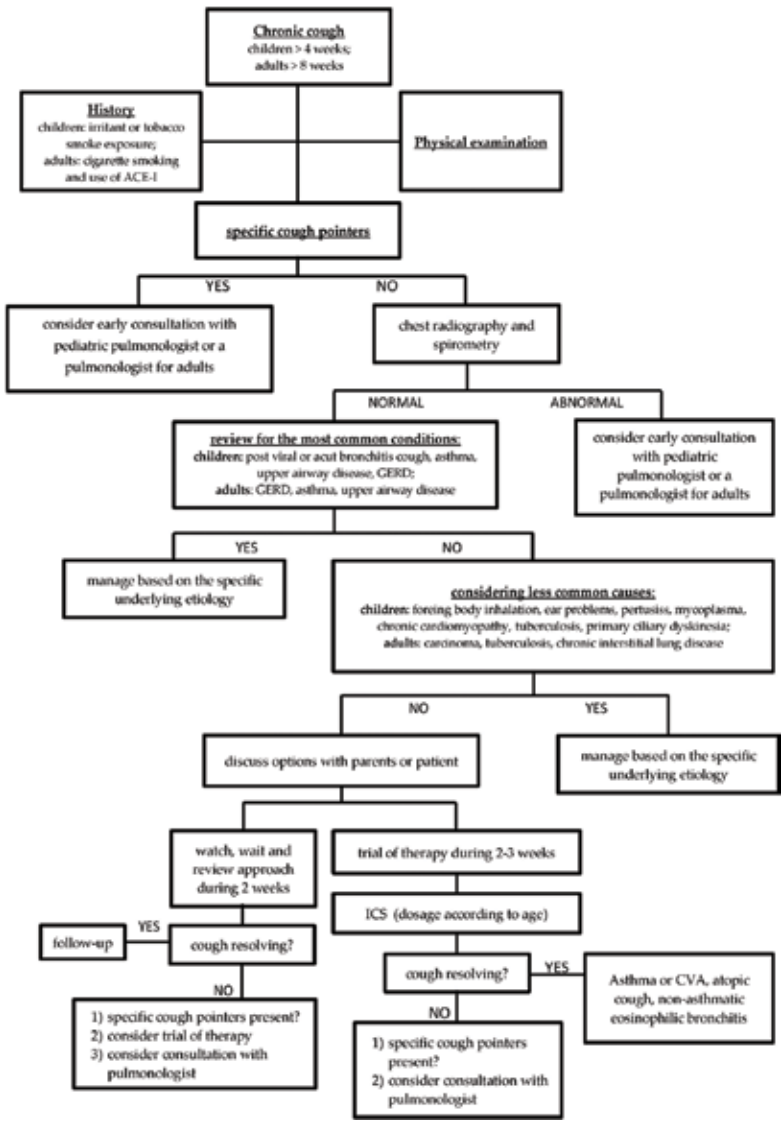

Figure 1. Algorithm for evaluation of chronic cough in children and adults for primary level doctors (general practitioner, pediatrician, family doctor, etc.).

cough in children under 14 are CVA, atopic cough, gastroesophageal reflux disease (GERD) and upper airway cough syndrome (formerly postnasal drip cough) [28–30]. CVA should be considered when chronic cough is exacerbated by cold or exercise [30]. Besides asthma and CVA in adult patients with chronic cough in the differential diagnosis, smoking and ACE-I induced a cough should always be considered [30]. Less common conditions include heart failure, interstitial lung disease, tuberculosis and primary lung cancer [26, 29, 31].

A few algorithms of the evaluation of chronic cough in adults and children are available in the literature [25, 30–32]. The use of these protocols or algorithms can improve clinical outcomes [28]. Most appropriated algorithm for adults can be found in a review article by Terasaki et al. [31]. In adults, the clinicians need to be attentive to two high-yield elements of the history patients: the use of an angiotensin-converting enzyme inhibitor (ACE-I) and cigarette smoking. Of equal importance is to inquire about exposure to second-hand smoke in children [25, 26, 31]. Most appropriated algorithm for children can be found in a review article by Chang et al. [25]. We have designed one of the algorithms that can be used as a guide for the primary level physicians (**Figure 1**).

Initial diagnostic evaluation should include the chest radiograph and pulmonary function testing in patients with chronic cough [25, 29–31]. It is not recommended to routinely performing additional tests (skin prick test, bronchoscopy, chest CT) for all children with chronic cough. Additional tests should be individualized and undertaken in accordance with the clinical symptoms and signs [29]. Chronic cough suggestive of serious underlying lung disease includes neonatal onset of cough [30].

It is recommended that in case of inadequate response to inhalation therapy, it should try with the inhalation therapy through an aerochamber which can help to maximize drug delivery to the lungs [31].

In a clinical evaluation of patients with chronic cough, it can be tried with the diagnosis *ex juvantibus*. There are no agreement about recommendations how long to use a particular therapy and wait for a therapeutic response to confirm the diagnosis *ex juvantibus* [25, 29, 31].

7. Conclusion

The CVA has the same pathophysiological features as classical asthma but in a mild form. The main pathophysiology of CVA is bronchial hyperreactivity.

Since a large percentage of patients with CVA develop classical asthma and wheezing over time, ICS treatment in these patients is very important because of the prevention of classical asthma development. One very important diagnostic criterion in CVA patients is an improvement of the symptoms after bronchodilator therapy. The positive therapeutic effect of ICS on cough in children with CVA should not be considered as a diagnostic criterion because the positive therapeutic effect also has patients with atopic cough [8].

"In children with chronic cough parental expectations should be determined, and the specific concerns of the parents should be sought and addressed" [25].

Author details

Sanela Domuz Vujnović[1]*, Adrijana Domuz[2] and Slobodanka Petrović[3]

*Address all correspondence to: drdomuz@gmail.com

1 School of Applied Medical Sciences, Prijedor, Republic of Srpska, Bosnia and Herzegovina

2 Primary Health Center, Ribnik, Republic of Srpska, Bosnia and Herzegovina

3 Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Republic of Srbija

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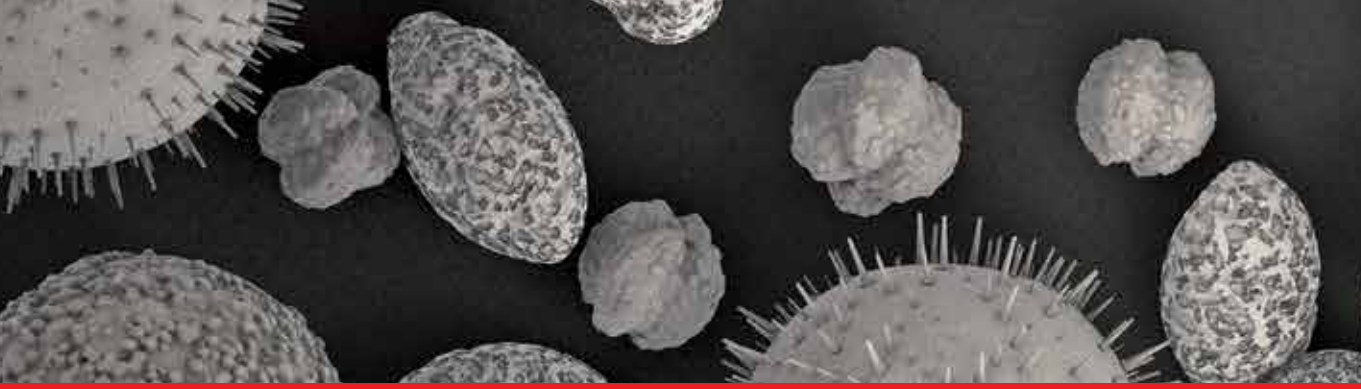

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Asthma is a severe and growing threat affecting both children and adults in both developing and developed world, currently affecting approximately 8% of US population. It is becoming increasingly recognized as a syndrome constituted by airway obstruction, airway hyperresponsiveness, and airway inflammation with different causes, associated risk factors, and underlying pathophysiology. The advances in basic and clinical research of asthma have accelerated over the past 20 years with increasing diagnostic tools, especially biomarkers, that led to specific characterization of individual patient's asthma pathophysiology, or disease "phenotype" and "endotype," which allowed precision medicine therapies, including new asthma biologics. This book aims to update the paradigm shifts in precision medicine of asthma diagnosis and management, driven by underlying phenotypes or endotypes.

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