JGG 2016;64:55-65

Review

Bronchial asthma in the elderly patient

L. Longobardi[1], A. Di Giorgio[1], F. Perrotta[1], A. Costigliola[1], F.S. Cerqua[1], G. Cioffi[1], I. Forzano[1], M. Flora[1], A. Cennamo[1], C. Iadevaia[1], C.M.E. Tranfa[1], F. Stefanelli[2]

[1] Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, Italy; [2] Division of Pneumology, AORN Dei Colli "Monaldi Hospital", Naples, Italy

Asthma is a heterogeneous chronic inflammatory lung disease originating from a complex interaction between individual and environmental factors. As consequence of world population ageing an increase of chronic diseases prevalence, including asthma, has been documented. Late-onset asthma may have more complex pathogenic mechanisms other than Th2-mediated pattern. Diagnosis in older subjects is not straightforward as consequence of poor symptoms perception; in adults co-morbidities are associated with different asthma outcomes. A careful assessment and management of all potential concurrent disorders is essential to achieve a better disease control and an adequate response to treatment in elderly asthmatic patients.

Key words: Asthma, Elderly, Late-onset

INTRODUCTION

The ageing of the world's population is, at least in part, the reason of increased prevalence of several chronic diseases, including asthma and chronic obstructive pulmonary disease [1].

In particular, asthma in the elderly is not a rare disorder and age-related changes in the dyspnea perception and the increasing of associated co-morbidities modify frequently its clinical presentation.

Asthma is a heterogeneous chronic inflammatory lung disease originating from a complex interaction between individual and environmental factors [2-12].

Main characteristics of asthma include bronchial hyperreactivity, reversible airflow obstruction, and tissue remodeling. The most frequent symptoms in asthmatic patients are recurrent coughing, dyspnea, chest tightness, shortness of breath and sporadic wheezing, which are also common to other respiratory diseases [13-15].

Symptoms may be triggered by several factors including respiratory infections, allergens, occupational exposures, tobacco smoke, exercise and stress; respiratory viruses are a major trigger for acute asthma exacerbations [1 6-22].

Diagnosis of asthma is made by a history of variable respiratory symptoms and evidence of variable expiratory airflow limitation. Pulmonary functional tests are essential for diagnosis; additional investigations include skin prick tests, IgE serum levels, FeNO whilst imaging procedures are more relevant for differential diagnosis [23-26].

As consequence of poor symptoms perception asthma, in the elderly, may be under-diagnosed.

Asthma exhibits multiple phenotypes arising from different clinical features and biological pathways including those involved in metabolic dysregulation [27-29].

In order to obtain effective treatment, it is important to determine the specific type of asthma. Atopic asthma is commonly characterized by type 2 helper T cell (Th2) cytokine-induced eosinophilic inflammations in the airway [30-32]. Some studies showed a strong link between genetic predisposition and early-onset of asthma [32].

Received: May 5, 2016 – Accepted June 17, 2016

Correspondence: Fabio Perrotta, Department of Cardio-Thoracic and Respiratory Sciences - Second University of Naples, Monaldi Hospital, via L. Bianchi, 80131 Naples, Italy - Tel. +39 081 5453017 - E-mail: perrotta572@msn.com

Allergic asthma commonly starts in youth and may either remit or recur in adulthood [33]; it is characterized by mast cell degranulation, amplified goblet cell hyperplasia, thickening of the sub-epithelial basement membrane, and epithelial damage [34]. By contrast, non-atopic asthma which exhibit a late disease onset and is prevalent in elderly patients, usually may display high levels of serum and sputum neutrophils [35].

Most children with persistent asthma phenotype exhibit current symptoms in adulthood, whilst around half reach remission [36]. In asthmatic children who become asymptomatic in adolescence and have a recurrence of asthma in adulthood, the disease may be misclassified as "adult-onset asthma" [37 38].

Compared to childhood-onset asthma, asthma of adult onset is prevalent among nonatopic females and shows a more severe decline in lung function despite a shorter duration of disease [39 40]. Indeed, in terms of lung function, non-atopic asthma may be even more detrimental than atopic asthma [35]. The adult-onset asthma phenotype is associated with greater corticosteroid resistance when compared with youth's eosinophilic asthma [41].

In addition, elderly patients have low serum immunoglobulin E (IgE) levels due to immunosenescence; therefore, measurement of total serum IgE for clinical asthma diagnosis is less effective [35].

Age-related changes in the respiratory system may contribute to clinical features of the disease: reduced diaphragmatic force generation and systemic inflammatory changes may occur in the elderly causing an accelerate functional decline [42].

EPIDEMIOLOGY

Asthma causes a significant public health burden and can manifest itself in any age [43].

According to the World Health Organization, 4.3% of adults around the globe received a diagnosis of asthma [44].

Adult-onset asthma has become much more prevalent recently and is now an important public health concern due to its severity and lower remission rate [45]. The mortality is high in the elderly population [46]. Older asthmatic patients typically have more severe symptoms than younger ones requiring emergency treatment or hospital admission [47]. Asthma in the elderly can be misdiagnosed or under-diagnosed due to the under-reporting of symptoms, atypical presentation, or age-related factors [48 49]. For example, dyspnea, which is one of the most common symptoms in asthmatic patients, can be considered as an age-related reduction in respiratory efficiency. In addition, in older adults, a poor response to bronchodilators, the absence of an atopic history, low skin test sensitivity, and a lack of recognized diagnostic contribute to the under-diagnosis of asthma in the elderly [50-56].

Furthermore, to avoid misdiagnoses, it is important to discriminate asthma from other airway diseases with similar features. For example, it can be difficult to discriminate COPD from asthma in older patients since both diseases are characterized by airway obstruction and dyspnea; a large number of neutrophils are associated with both COPD and non-atopic asthma [57 58].

Moreover, owing to a large number of comorbidities in the elderly, it has been observed that asthmatic symptoms in these patients have been wrongly attributed to comorbid conditions such as congestive heart failure, coronary artery disease or chronic bronchitis (Fig. 1) [42 50]. Comorbidities, such as obesity and heart disease, can confound but also complicate asthma and leave it under-diagnosed or difficult to treat [59-61], also because drugs targeting these comorbidities may interfere with asthma medications and exacerbate asthma in the elderly (Fig. 2).

In a study by Piipari et al. [62] current smokers and ex-smokers had a significantly higher risk of developing asthma compared with those who have never smoked. The authors concluded that smoking highly increases the risk of asthma in adulthood.

PATHOGENESIS AND IMMUNOSENESCENCE

Increased reactive oxygen species (ROS) levels strongly correlate with the severity of asthma [63]. These higher amounts of ROS are largely responsible for the airway inflammation observed in asthma [64]. ROS and reactive nitrogen species (RNS) play an important role during airway inflammation (65). ROS/RNS initiate the inflammatory response in the lungs by activating nuclear factor-kappa B (NF-$\varkappa$B), mitogen activated protein kinase (MAPK), activator protein-1 (AP-1), and other transcription factors [65 66]. These redox-sensitive transcription factors promote the expression of numerous pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)- 1, IL-6, and IL-8, which induce the activation of inflammatory cells within the respiratory tract [67]. Interestingly, it seems that these inflammatory cells including macrophages, eosinophils, neutrophils, and monocytes are able to generate ROS themselves in order to kill the invading bacteria [68].

In elderly adults, the lower ability of neutrophils to kill invading organisms can be attributed to a decline in their ROS production. For this reason, elderly patients are more predisposed to a variety of infections and diseases.

Bacterial stimulation of the immune system is related to

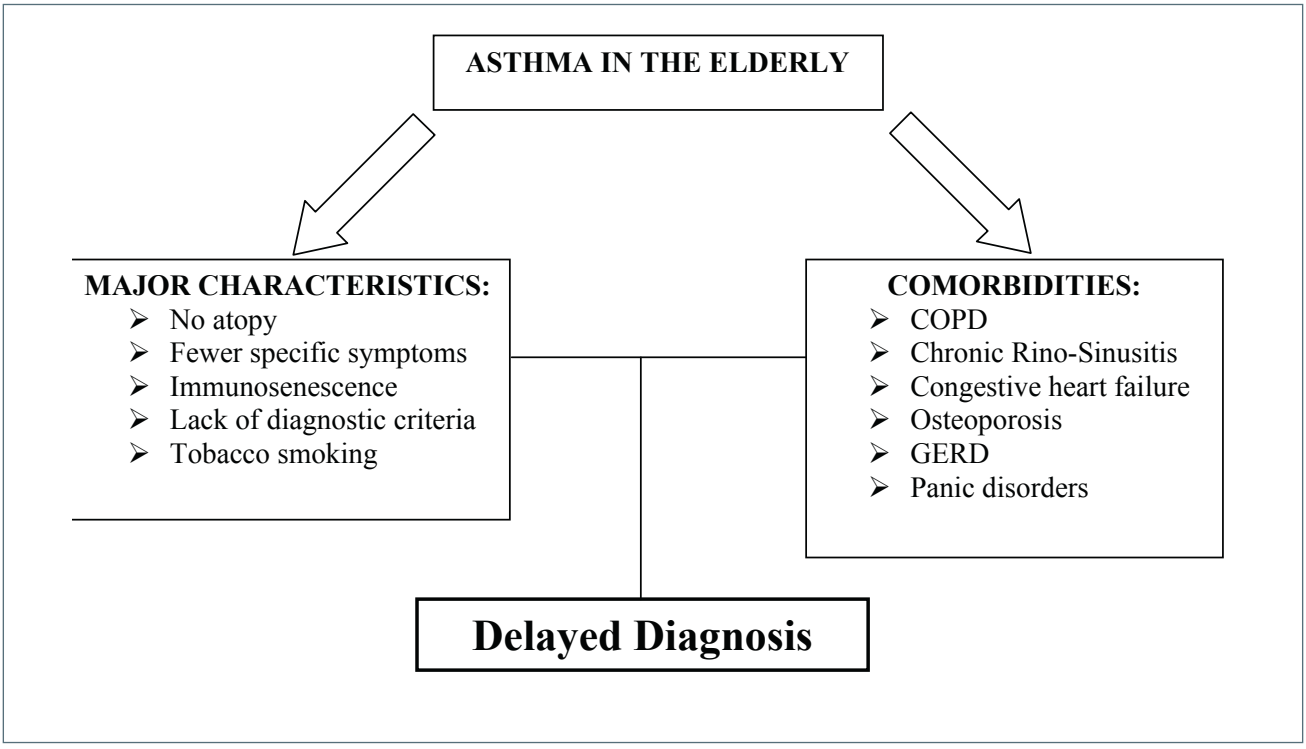

Figure 1. Asthma characteristics in elderly patients.

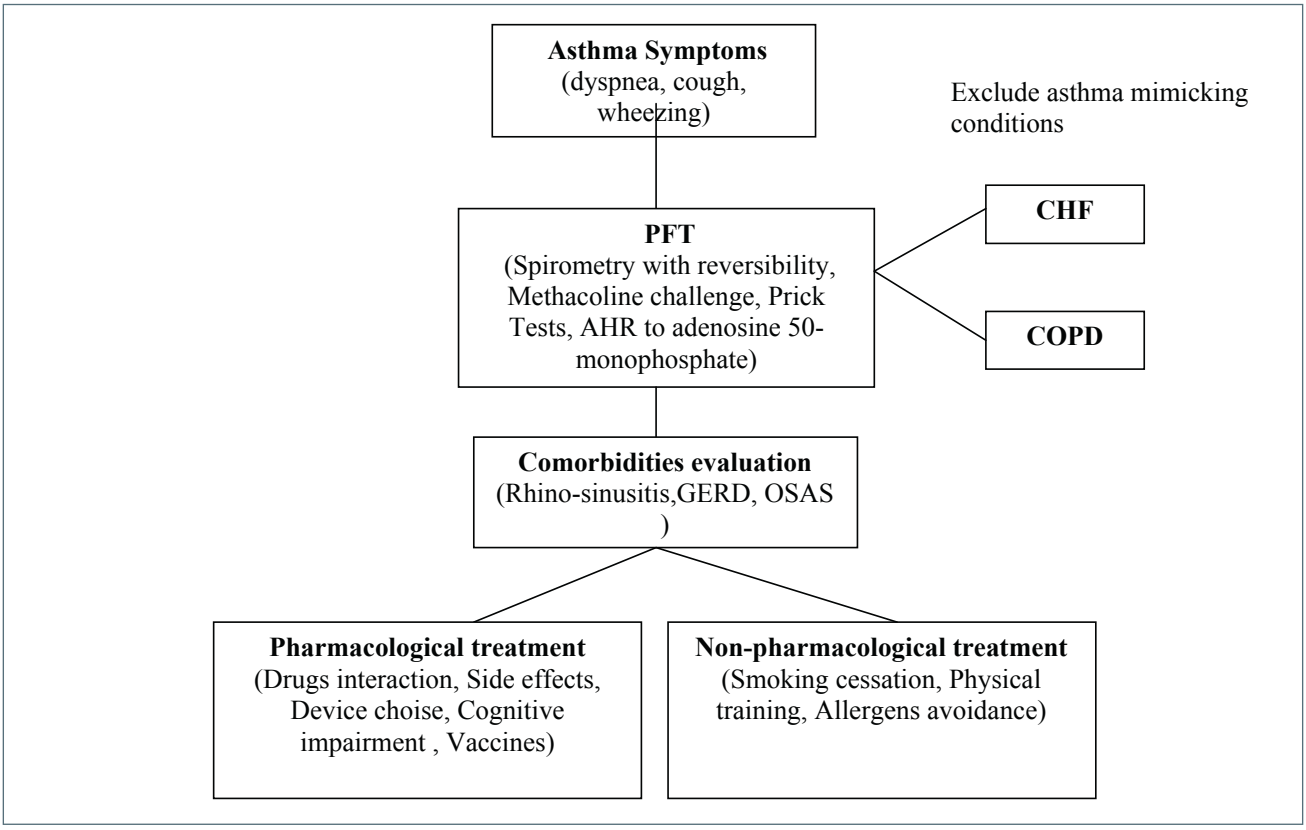

Figure 2. Diagnostic approach to asthma in older adults.

stimulation of the innate immune system and Th1 and Th17 activation in the adaptive response, it is recognized that bacterial products, such as superantigens, may be related to Th2-mediated inflammation.

Staphylococcus aureus (SA) is one of the most frequent human bacterial pathogens producing enterotoxins (SE) that act as toxins as well as superantigens.

The prevalence of SE sIgE positivity among asthmatics population varied with study populations, ranging from 14.9% to 79.1%; however, the rates showed trends to increase in older subjects and in more severe asthmatics. In non-asthmatic controls, the rate of SE sensitization also ranged widely, from 3.8% to 41.3% [69].

Older age is apparently a clinical factor to link asthma and SE sIgE. In older adult asthma, eosinophilic airway inflammation is frequently observed while no serum sIgE is detectable for common inhalant allergens. Some studies hypothesize that Th2 responses to inhaled bacterial antigens may contribute to non-atopic eosinophilic asthma in older adults. Severe asthma is another subtype which is related to SE sIgE, as suggested by two recent case-control studies [70 71].

Staphylococcus aureus commonly colonizes the human nasal mucosa, and the enterotoxins there of may provoke chronic rinosinusithis (CRS) and nasal polyp development.

FurthermoreSE-IgE sensitization is independently associated with inadequate outcomes and asthma severity in non-atopic adult patients and with severe eosinophilic asthma in the elderly [72].

Many clinical trials suggest a potential role of SA superantigens in the persistence and severity of asthma and allergic rhinitis. Bachert et al. [73] show that SE-specific IgE were more commonly found in patients with severe asthma (as assessed by measurement of FEV1, need for inhaled or oral steroid treatment, and serum level of ECP) compared to controls (62% *vs* 13%, P = 0.01).

Song et al. in their systematic review show that SE sensitization has significant associations with asthma, and in particularly, it was suggested to have relationships with the clinical reactivity and severity of asthma [69]. Immunosenescence includes age-related functional declines in the innate and adaptive immune systems [74 75]. However, the effects on adaptive immunity are more well-known than on innate immunity. Probably, altered immune responses may facilitate the pathogenesis of asthma in the elderly [76].

ASTHMA COPD OVERLAP SYNDROME (ACOS)

Obstructive ventilatory defects are a considerable challenge in elderly patients. Asthma and COPD are two major chronic obstructive airway diseases, but many patients present symptoms and features of both asthma and COPD. A graphic representation of this relationship was first presented as the non-proportional Venn diagram, reported in the 1995 American Thoracic Society (ATS) COPD guidelines [77]. In 2007 and subsequently in 2012, the Canadian and Spanish [78 79] guidelines for COPD recognized that patients with COPD and an asthma component may require a different treatment and the early introduction of inhaled corticosteroids (ICS) represents the best therapeutic option. In 2014, a GINA-GOLD committee developed a consensus based document in order to distinguishing between asthma, COPD and the overlap of asthma and COPD, so called Asthma COPD Overlap Syndrome (ACOS). In this manuscript, ACOS was described as a complex syndrome that usually involves adults (≥ 40 years), characterized by respiratory symptoms, persistent airflow obstruction with wide variations, history of doctor-diagnosed asthma, allergies and history of noxious exposures [80]. Louie et al. [81] defined ACOS as one of the two clinical phenotypes: asthma with partially reversible airflow obstruction, with or without emphysema or reduced carbon monoxide diffusing capacity (DLCO) to less than 80% predicted, and COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced DLCO. Several studies reported that ACOS becomes more prevalent in older patients [82 83]. Probably, this is due to a lifetime exposure to atmospheric pollution and environmental tobacco smoke in association to physiological changes in the lungs [7-12]. ACOS patients have more respiratory symptoms, such as dyspnea and wheezing, reduced physical activity and more frequent exacerbations compared with patients with COPD alone [84]. They also have a lower self-rated health and more impaired health-related quality of life compared with COPD. As a consequence, ACOS patients consume from 2 to 6-fold more healthcare resources than those used by asthma or COPD patients [85]. The combination of pulmonary function tests and chest HRCT showed that asthmatic elderly patients could be classificated into three different phenotypes: asthma-predominant (absence of airflow obstruction), asthma-obstructive airways disease overlap (irreversible airway obstruction without emphysema) and asthma-emphysema overlap (combination of obstructive ventilatory defect and emphysema).

Bronchial Hyper-responsiveness

Bronchial hyper-responsiveness (BHR) is often regarded as a 'hallmark' of asthma, also in the elderly. Bronchial hyper-responsiveness indicates a temporary airflow limitation when exposed to a broncho-constriction stimulus and broncho-provocation testing is frequently performed to support a diagnosis of asthma. The most

widely used is the methacholine challenge test, but histamine, exercise, eucapnic voluntary hyperventilation or inhaled mannitol tests may also be used. These tests are moderately sensitive for the diagnosis of asthma but are commonly poor specific. For example, BHR to methacoline can be found in COPD, allergic rhinitis, gastro-esophageal reflux and after viral or Mycoplasma infection

Methacholine BHR exhibits a bi-modal age distribution in the general population, increasing in the elderly, and may contribute to accelerated lung function decline and the development of asthma in later stages of life. For this reason we believe it would be helpful in elderly patients who has a mild obstruction, not reversible (FEV1 > 70%, even with history favoring the diagnosis of COPD (smoker, onset of respiratory symptoms in adulthood, radiological signs of emphysema) a methacholine challenge; the positivity to this test may involve a detachment from what is recommended by current COPD guidelines, since the presence of BHR will require treatment with inhaled steroids, in addition to a bronchodilatator (LABA o LAMA). A usefull test in diagnostic of obstructive diseases could be represented by airway hyperresponsiveness (AHR) to adenosine 50-monophosphate. Spicuzza et al. [86] showed that a single dose of inhaled fluticasone propionate (1000 mg) on AHR to inhaled AMP is able to distinguish in subjects with asthma and COPD; infact, FP caused a substantial reduction in the bronchoconstrictor response to AMP in subjects with asthma but not COPD.

IMPACT OF COMORBIDITIES IN ASTHMA ELDERLY PATIENTS

Rhinitis and rhinosinusitis

Asthma and rhinitis are considered as two different features of the same airway disease and are commonly associated to atopy.

A growing body of clinical-epidemiological investigations indicate a close relationship between asthma and allergic rhinitis. According to cross-sectional studies [87] asthma and rhinitis often coexist and share common risk factors, including atopy.

Several mechanisms might be responsible for the interaction between the upper and lower airways in asthmatic individuals; both respiratory and systemic pathways are implicated in the naso-bronchial cross-talk [88]. Loss of protective functions of the nose, aspiration of nasal secretions in lower airways (post-nasal drip), alteration of nasal nitric oxide (NO) production have been associated to lower airway dysfunctions.

Despite the small number of studies, a relationship between asthma and chronic rhino-sinusitis (CRS) has been reported in elderly patients. Song et al. observed that CRS is an independent risk factor for frequent asthma exacerbation and disease severity in elderly patients [72]. In addition, Jarvis et al. [89] showed that non-atopic CRS was positively associated with adult-onset asthma.

In patients with late-onset asthma, nasal polyposis and sinusitis have been strongly associated to severe asthma outcome. In the Severe Asthma Research Program (SARP), 54% of patients with severe asthma had a history of sinusitis *vs* 33% of those with mild asthma, and 37% of those with moderate asthma ($P < 0.001$) [90]. Also, a meta-analysis focusing the role of sinus surgery among patients with asthma has revealed that surgery had positive effects on the clinical course of asthma with comorbid chronic rhino-sinusitis [91].

These evidences indicates that disease of upper airway may influence the onset and severity of asthma and in particular appears to be associated to poor outcomes in adult-onset asthma.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a major upper gastrointestinal disorder seen in the elderly. In older subjects, there is a considerable decrease in the amplitude of peristaltic contraction and an increase in the frequency of non-propulsive and repetitive contractions compared to younger individuals, often referred to as presbyesophagus [92]. Salivary production slightly decreases with age and is associated with a lower salivary bicarbonate response to acid perfusion of the esophagus [93]. Finally, many drugs and diseases may adversely affect esophageal motility. In particular LES, Parkinson's disease, diabetes mellitus, cerebro-vascular, cardiovascular and pulmonary diseases are associated to esophageal dismotility. Asthma is associated with GERD in 12 to 85% of patients; the wide variation is dependent on the method used to define GERD [94]. Although an association between gastro-esophageal reflux disease (GERD) and asthma has also been reported, the underlying mechanism of this relationship remain unclear. The development of pulmonary complications in GERD is due not only to the pulmonary aspiration of refluxed material but also involves a neurally mediated reflex bronchoconstriction due to esophageal irritation by acid [95]. However, inconsistent results have been obtained in several studies on the effects of treatment of GERD on asthma outcomes. In 2003, Gibson et al. [96] showed that anti-reflux therapy did not consistently improve lung function, asthma symptoms, nocturnal asthma or the use of asthma medications. By contrast, some studies reported that PPI therapy

improves nocturnal asthma symptoms, daytime asthma symptoms, pulmonary function and decreases requirement of asthma medications in patients with GERD [97]. In elderly asthmatic patients although definitive remarks require further observations, GERD diagnosis should be considered in patients with poor symptoms control.

Sleep disturbances (SD) and OSAS

Sleep disturbances (SD), and OSAS in particular, are a common finding in patients with late asthma onset impacting on quality of life (QoL) and clinical course of the disease. OSAS is characterized by repeated episodes of upper airways occlusion that results in brief periods of breathing cessation (apnea) or a marked reduction in flow (hypopnea) during sleep. This pattern is related to oxyhemoglobin desaturation, persistent inspiratory efforts against the occluded airway, and arousal from sleep. The prevalence of OSAS increases with age, independently from other risk factors [98].

The first case reporting a possible link between asthma and OSAS was published in 1979, by Hudgel and Shruchard. Over the years more evidence were added to the knowledge about this topic. Many mechanisms may influence asthma control in patients with concomitant OSAS, including neuro-mechanical reflex bronchoconstriction, gastro-esophageal reflux, systemic inflammation.

In OSAS patients, the increased vagal tone observed occurring during apneas and could be a potential trigger for nocturnal asthma attacks in sleep apnea patients. An additional broncho-constrictive trigger is represented by hypoxia stimulation of the carotid body as results of obstructive apnea events.

OSAS patients have a higher incidence of gastroesophageal reflux. It is postulated that the increase in negative intra-thoracic pressure caused by upper airway obstruction can predispose to retrograde movement of gastric contents. GER occurring during sleep is a well-known trigger for nocturnal asthma and can provoke asthma symptoms through vagal reflexes induced by exposure of the esophagus to acid.

In individuals with OSAS, even in the absence of an inflammatory insult, chronic, low-grade systemic inflammation is characterized by increased serum concentrations of cytokines, and chemokines [99]. The origin of this systemic inflammation appears to be, at least in part, the oxidative stress induced by oxygen desaturation during sleep apneas.

OSAS has been shown to lead to many cardiovascular consequences, which may complicate a co-existing airway obstruction in asthmatic patients.

Another cause of the high incidence of OSAS in asthmatic patients may be the reduction of airway cross-sectional area and upper airway patency; the functional residual capacity of the asthmatics has been show to decline during sleep, which might partly contribute to the nocturnal increase in airway resistance [100].

A vicious cycle among GERD, obesity, cardiovascular diseases, systemic inflammation seems to contribute to worsens sleep apnea, which leads to increased severity of both asthma and OSAS.

RISK FACTORS FOR ADULT-ONSET ASTHMA

Late-onset asthma may have more complex pathogenic mechanisms other than the conventional Th2-mediated pattern which is largely mediated by atopy conditions. In adults a number of comorbid conditions are associated with different asthma outcomes (Tab. I).

Depression

Depression commonly coexists with asthma and is associated with more severe asthma and poorer asthma management. Coogan et al. reported that exists a positive association between CES-D (Center for Epidemiological Studies-Depression Scale) score and incidence of adult-onset asthma [101].

Some data suggest that depressed or sad moods elicited under laboratory conditions can produce pulmonary effects consistent with decreased airway function [102 103].

Stress is a recognized trigger of asthma exacerbation [(104)] and may cause poor adherence to asthma treatment. Conversely, remission from depression is associated with improved asthma control

The mechanism by which depression may “cause” asthma in unclear. Multiple pathways have been hypothesized: it seems that stress effects on the immune and autonomic nervous systems are relevant to the development of asthma [105], as well as co-existence of common comorbidities and inflammatory/neuroendocrine mechanisms. Major depressive disorder leads to alteration in the hypothalamic-pituitary-adrenal axis that results in endogenous glucocorticoid resistance. This, in turn, could increase vulnerability to asthma onset by biasing the immune system toward a T helper type 2 response [106 107].

Menopause

Menopause is associated with relevant hormonal and metabolic changes: estrogen levels are low after menopause, and features of the metabolic syndrome become more prevalent paired with increasing risk of chronic conditions, such as diabetes and cardiovascular diseases [108]. It has been suggested that late-onset asthma can be triggered by a change in systemic inflammation [109 110].

Sex hormone reduction has been found to be associated with a spontaneous synthesis, release, and action of

Table I. Clinical and therapeutical issues of comorbidities in elderly asthmatic patient. Impact of comorbidities on asthma outcomes.

Comorbidities		Asthma outcomes	Pathophysiology	Treatment reccomendations
Related to ageing	Depression	• Poor adherence to asthma treatment • Increase of asthma exacerbations	• Stress effects on the immune and autonomic nervous systems • Inflammatory/neuroendocrine mechanisms	Assess to avoid drug interaction or treatment failure
	Cognitive impairment	• Poor adherence to asthma treatment • Altered perception of symptoms		
	Menopause	• More frequent and severe exacerbations	• Low estrogen levels • Increase of systemic inflammation • Increasing risk of chronic conditions	
Related to shared risk factors	Rhinitis and rhinosinusitis	• Increase of asthma exacerbations • Increased severity of both asthma	• Loss of protective functions of the nose • Aspiration of nasal secretions in lower airways (post-nasal drip) • Alteration of nasal nitric oxide (NO) production	Treat independently to improve asthma outcomes
	Gastroesophageal reflux disease (GERD)	• Increase of asthma symptoms • Nocturnal asthma • Pulmonary complications	• Pulmonary aspiration of refluxed material • Neurally mediated reflex bronchoconstriction due to esophageal irritation by acid	
	Sleep disturbances (SD) and OSAS	• Increase of nocturnal asthma attacks • Increased severity of both asthma	• Neuro-mechanical reflex broncho-constriction (increased vagal tone) • Gastro-esophageal reflux • Systemic inflammation	
	COPD (Asthma copd overlap syndrome - ACOS)	• More respiratory symptoms (dyspnea and wheezing) • Reduced physical activity • More frequent exacerbations • Impaired health-related quality of life	• Persistent airflow obstruction with wide variations • History of doctor-diagnosed asthma and allergies • History of noxious exposures	
	Congestive Heart Failure and Cardiac Asthma	• Symptoms of acute and chronic cardiac and respiratory illnesses overlap • Wheezing, coughing and orthopnea	• Pulmonary edema • Pulmonary vascular congestion • Airway obstruction is probably amplified by circulating inflammatory factors and tissue growth factors	

several inflammatory cytokines [111]. Foschino-Barbaro et al. described a new phenotype of menopausal asthma, which is mainly characterized by a neutrophilic airway inflammation, non-sensitivity to steroids, poor symptom control, and higher levels of LTE-4 [112].

Airways inflammation in postmenopausal asthmatic patients seems to be different from that of patients with earlier-onset asthma, and is characterized by poorer response to anti-inflammatory treatment, as well as more frequent and severe exacerbations [110].

CONCLUSIONS

Asthma diagnosis in older subjects is not straightforward and under-diagnosis may occur as consequence of poor symptoms perception.

A multidisciplinary approach is required as co-morbidities are frequently associated to asthma in elderly patients. A careful assessment and management of all potential concurrent disorders is essential to achieve a better asthma control and an adequate response to treatment.

Performing metacholine challenge test is central to clinical disease management, also in elderly asthmatic patients; metacholine BHR seems, indeed, to be very common in old patients, with relevant implications in terms of appropriate treatment.

In this regard, significant progress in the management of asthma in the elderly could be made by introducing a tests that discriminate between asthma and COPD bronchial hyper responsiveness trough using adenosine 50-monophosphate; a single dose of inhaled

fluticasone propionate (1000 mg) on adenosine's AHR has been shown to determine a remarkable reduction in the bronchoconstriction in asthmatic subjects but not in patients with COPD [86].

Finally, the approach to asthmatic patients requires to consider the role of *S. Aureus* that seems to be largely implicated in older patients causing more severe symptoms, major airway hyperresponsiveness and worse control of the disease. For these reasons, a specific treatment against SA need to be considered to improve asthma management of in the elderly.

References

1 Cacciatore F, Gallo C, Ferrara N, et al. *Morbidity patterns in aged population in southern Italy. A survey sampling.* Arch Gerontol Geriatr 1998;26:201-13.

2 Fryer AA, Bianco A, Hepple M, et al. *Polymorphism at the glutathione S-transferase GSTP1 locus. A new marker for bronchial hyperresponsiveness and asthma.* Am J Respir Crit Care Med 2000;161:1437-42.

3 Fryer AA, Spiteri MA, Bianco A, et al. *The -403 G–> A promoter polymorphism in the RANTES gene is associated with atopy and asthma.* Genes Immun 2000;11:509-14.

4 Spiteri MA, Bianco A, Strange RC, et al. *Polymorphisms at the glutathione S-transferase, GSTP1 locus: a novel mechanism for susceptibility and development of atopic airway inflammation.* Allergy 2000;55:15-20.

5 Mazzarella G, Petillo O, Margarucci S, et al. *Role of monocyte/macrophage population in immune response.* Monaldi Arch Chest Dis 1998;53:92-6.

6 Catena E, Mazzarella G, Peluso GF, et al. *Phenotypic features and secretory pattern of alveolar macrophages in atopic asthmatic patients.* Monaldi Arch Chest Dis 1993;48:6-15.

7 Mazzarella G, Esposito V, Bianco A, et al. *Inflammatory effects on human lung epithelial cells after exposure to diesel exhaust micron sub particles (PM1.0) and pollen allergens.* Environ Pollut 2012;161:64-9.

8 Mazzarella G, Lucariello A, Bianco A, et al. *Exposure to submicron particles (PM1.0) from diesel exhaust and pollen allergens of human lung epithelial cells induces morphological changes of mitochondria tonifilaments and rough endoplasmic reticulum*. In Vivo 2014;28:557-61.

9 Mazzarella G, Ferraraccio F, Prati MV, et al. *Effects of diesel exhaust particles on human lungepithelialcells: an in vitro study.* Respir Med 2007;101:1155e1162.

10 De Laurentiis G, Paris D, Melck D, et al. *Separating smoking-related diseases using NMR-based metabolomics of exhaled breath condensate.* J Proteome Res 2013;12:1502-11.

11 Grella E, Paciocco G, Caterino U, et al. *Respiratory function and atmospheric pollution*. Monaldi Arch Chest Dis 2002;57:196-9.

12 Esposito V, Lucariello A, Savarese L, et al. *Morphology changes in human lung epithelial cells after exposure to diesel exhaust micron sub particles (PM1.0) and pollen allergens.* Environ Pollut 2012;171:162-7.

13 Urso DL. *Asthma in the elderly*. Curr Gerontol Geriatr Res 2009:858415.

14 Boulet LP, Becker A, Berube Det al; Canadian Asthma Consensus Group. *Canadian Asthma Consensus Report, 1999*. CMAJ 1999;161(Suppl 11):S1-61.

15 Mazzarella G, Iadevaia C, Guerra G, et al. *Intralobarpulmonary sequestration in an adult female patient mimicking asthma: a case report*. Int J Surg 2014;12(Suppl 2):S73-7.

16 Whiteman SC, Bianco A, Knight RA, et al. *Human rhinovirus selectively modulates membranous and soluble forms of its intercellular adhesion molecule-1 (ICAM-1) receptor to promote epithelial cell infectivity.* J Biol Chem 2003;278:11954-61.

17 Bianco A, Whiteman SC, Sethi SK, et al. *Expression of intercellular adhesion molecule-1 (ICAM-1) in nasal epithelial cells of atopic subjects: a mechanism for increased rhinovirus infection?* Clin Exp Immunol 2000;121:339-45.

18 Micillo E, Bianco A, D'Auria D, et al. *Respiratory infections and asthma*. Allergy 2000;55:42-5.

19 Sethi SK, Bianco A, Allen JT, et al. *Interferon-gamma (IFN-gamma) down-regulates the rhinovirus-induced expression of intercellular adhesion molecule-1 (ICAM-1) on human airway epithelial cells*. Clin Exp Immunol 1997;110:362-9.

20 Bianco A, Sethi SK, Allen JT, et al. *Th2 cytokines exert a dominant influence on epithelial cell expression of the major group human rhinovirus receptor, ICAM-1*. Eur Respir J 1998;12:619-26.

21 Bianco A, Parrella R, Esposito V, et al. *Severe A(H1N1)-associated pneumonia sequential to Clamidophila pneumoniae infection in healthy subject*. In Vivo 2011;25:825-8.

22 Bianco A, Mazzarella G, Bresciani M, et al. *Virus-induced asthma*. Monaldi Arch Chest Dis 2002;57:188-90.

23 Izzo A, Perrotta F, Cennamo A. et al. *Spirometry in elderly laryngectomized patients: A feasibility study.* Int J Surg 2016 May 30. pii: S1743-9191(16)30144-3. doi: 10.1016/j.ijsu.2016.05.058. [Epub ahead of print]

24 Del Giudice G, Bianco A, Cennamo A, et al. *Lung and nodal involvement in nontuberculous mycobacterial disease: PET/CT Role*. Biomed Res Int 2015;2015:353202.

25 Bianco A, Mazzarella G, Rocco D, et al. *FDG/PET uptake in asymptomati cmultilobar* Chlamydia pneumoniae *pneumonia.* Med SciMonit 2010;16:CS67-70

26 Brunese L, Greco B, Setola FR, et al. *Non-small cell lung cancer evaluated with quantitative contrast-enhanced CT and PET-CT: net enhancement and standardized uptake values are related to tumour size and histology.* Med SciMonit 2013;19:95-101.

27 Nigro E. Scudiero O. Sarnataro D. et al. *Adiponectin affects lung epithelial A549 cell viability counteracting TNFα and IL-1s toxicity through AdipoR1*. Int J Biochem Cell Biol 2013;45: 1145-5331.

28 Nigro E, Scudiero O, Monaco ML, et al. *New insight into adiponectin role in obesity and obesity-related diseases*. Biomed Res Int 2014;2014:658913.

[29] Nigro E, Daniele A, Scudiero O, et al. *Adiponectin in asthma: implications for phenotyping*. Curr Protein Pept Sci 2015;16:182-7.

[30] Mazzarella G, Bianco A, Catena E, et al. *Th1/Th2 lymphocyte polarization in asthma.* Allergy 2000;55 (Suppl 61):6-9.

[31] Bartemes KR, Iijima K, Kobayashi T, et al. *IL-33-responsive lineage- CD25+ CD44(hi) lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs*. J Immunol 2012;188:1503-13.

[32] Wenzel SE. *Asthma phenotypes: the evolution from clinical to molecular approaches*. Nat Med 2012;18:716-25.

[33] Abramson MJ, Perret JL, Dharmage SC, et al. *Distinguishing adult-onset asthma from COPD: a review and a new approach.* Int J Chron Obstruct Pulm Dis 2014;9:945-62.

[34] Zuo L, Koozechian MS, Chen LL. *Characterization of reactive nitrogen species in allergic asthma.* Ann Allergy Asthma Immunol 2014;112:18-22.

[35] Rufo J, Taborda-Barata L, Lourenco O. *Serum biomarkers in elderly asthma*. J Asthma 2013;50:1011-9.

[36] Tai A, Tran H, Roberts M, et al. *Outcomes of childhood asthma to the age of 50 years*. J Allergy Clin Immunol 2014;133:1572-8.

[37] Martin AJ, McLennan LA, Phelan PD. *The natural history of asthma from childhood to adult life*. Br Med J 1980;280:1397-400.

[38] Burgess JA, Walters EH, Byrnes GB, et al. *Who remembers whether they had asthma as children?* J Asthma 2006;43:727-30.

[39] Miranda C, Busacker A, Balzar S, et al. *Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation.* J Allergy Clin Immunol 2004;113:101-8.

[40] Perret JL, Dharmage SC, Matheson MC, et al*. The interplay between the effects of lifetime asthma, smoking, and atopy on fixed airflow obstruction in middle age*. Am J Respir Crit Care Med 2013;187:42-8.

[41] Haldar P, Pavord ID. *Noneosinophilic asthma: a distinct clinical and pathologic phenotype*. J Allergy ClinImmunol 2007;119:1043-52; quiz 1053.

[42] Gibson PG, McDonald VM, Marks GB. *Asthma in older adults.* Lancet 2010;376:803-13.

[43] Ripabelli G, Tamburro M, Sammarco ML, et al. *Asthma prevalence and risk factors among children and adolescents living around an industrial area: a cross-sectional study*. BMC Public Health 2013;13:1038.

[44] Follenweider LM, Lambertino A. *Epidemiology of asthma in the United States*. Nurs Clin North Am 2013;48:1-10.

[45] Castiglia D, Battaglia S, Benfante A, et al. *Pharmacological management of elderly patients with asthma-chronic obstructive pulmonary disease overlap syndrome: room for speculation?* Drugs Aging 2016 Apr 30. [Epub ahead of print].

[46] Diette GB, Krishnan JA, Dominici F, et al. *Asthma in older patients: factors associated with hospitalization.* Arch Intern Med 2002;162:1123-32.

[47] Granell R, Henderson AJ, Sterne JA. *Associations of wheezing phenotypes with late asthma outcomes in the Avon longitudinal study of parents and children: a population-based birth cohort*. J Allergy Clin Immunol 2016 Apr 19. pii: S0091-6749(16)00383-3. doi: 10.1016/j.jaci.2016.01.046. [Epub ahead of print]

[48] Zuo L, Pannell BK, Liu Z. *Characterization and redox mechanism of asthma in the elderly*. Oncotarget 2016 Jan 29. doi: 10.18632/oncotarget.7075.

[49] Tzortzaki EG, Proklou A, Siafakas NM. *Asthma in the elderly: can we distinguish it from COPD?* J Allergy 2011;2011:843543.

[50] Bellia V, Battaglia S, Catalano F, et al. *Aging and disability affect misdiagnosis of COPD in elderly asthmatics: the SARA study*. Chest 2003;123:1066-72.

[51] Scichilone N, Callari A, Augugliaro G, et al. *The impact of age on prevalence of positive skin prick tests and specific IgE tests.* Respir Med 2011;105:651-8.

[52] Comella P, Frasci G, De Cataldis G, et al. *Cisplatin/carboplatin+etoposide+ vinorelbine in advanced non-small-celllungcancer: a multicentrerandomised trial*. Gruppo Oncologico Campano Br J Cancer 1996;74:1805-11.

[53] Piantedosi FV, Caputo F, Mazzarella G, et al. *Gemcitabine, ifosfamide and paclitaxel in advanced/metastatic non-small cell lung cancer patients: a phase II study*. Cancer Chemother Pharmacol 2008;61:803-7.

[54] Comella P, Frasci G, Panza N, et al. *Cisplatin, gemcitabine, and vinorelbine combination therapy in advanced non-small-cell lung cancer: a phase II randomized study of the southern Italy Cooperative oncology group.* J Clinical Oncol 1999;17:1526-34.

[55] De Simone G, Aquino G, Di Gioia C, et al. *Efficacy of aerobic physical retraining in a case of combined pulmonary fibrosis and emphysema syndrome: a case report*. J Med Case Rep 2015;9:85.

[56] Frasci G, Lorusso V, Panza N, et al. *Gemcitabine plus vinorelbine yields better survival outcome than vinorelbine alone in elderly patients with advanced non-small cell lung cancer*. *A Southern Italy Cooperative Oncology Group (SICOG) phase III trial.* Lung Cancer 2001;34(Suppl 4):S65-9.

[57] Athanazio R. *Airway disease: similarities and differences between asthma, COPD and bronchiectasis.* Clinics (Sao Paulo) 2012;67:1335-43.

[58] Buist AS. *Similarities and differences between asthma and chronic obstructive pulmonary disease: treatment and early outcomes*. Eur Respir J Suppl 2003;39:30s-5s.

[59] Bianco A, Mazzarella G, Turchiarelli V, et al. *Adiponectin: an attractive marker for metabolic disorders in Chronic Obstructive Pulmonary Disease (COPD).* Nutrients 2013;15:4115-25.

[60] Daniele A, De Rosa A, Nigro E, et al. *Adiponectin oligomerization state and adiponectin receptors airway expression in chronic obstructive pulmonary disease*. Int J Biochem Cell Biol 2012;44:563-9.

[61] Corbi G, Bianco A, Turchiarelli V, et al. *Potential mechanisms linking atherosclerosis and increased cardiovascular risk in COPD: Focus on sirtuins.* Int J Mol Sci 2013;14:12696-713.

[62] Piipari R, Jaakkola JJ, Jaakkola N, et al. *Smoking and asthma in adults*. Eur Respir J 2004;24:734-9.

[63] Sahiner UM, Birben E, Erzurum S, et al. *Oxidative stress in asthma*. World Allergy Organ J 2011;4:151-8.

[64] Zuo L, Otenbaker NP, Rose BA, et al. *Molecular mechanisms of reactive oxygen species-related pulmonary inflammation and asthma.* Mol Immunol 2013;56:57-63.

[65] Comhair SA, Erzurum SC. *Redox control of asthma: molecular mechanisms and therapeutic opportunities.* Antioxid Redox Signal 2010;12:93.

[66] Li N, Nel AE. *Role of the Nrf2-mediated signaling pathway as a negative regulator of inflammation: implications for the impact of particulate pollutants on asthma*. Antioxid Redox Signal 2006;8:88-98.

[67] Rahman I, Biswas SK, Kode A. *Oxidant and antioxidant balance in the airways and airway diseases.* Eur J Pharmacol 2006;533:222-39.

[68] Yatagai Y, Hirota T, Sakamoto T, et al. *Variants near the HLA complex group 22 gene (HCG22) confer increased susceptibility to late-onset asthma in Japanese populations.* J Allergy Clin Immunol 2016 Jan 30. pii: S0091-6749(16)00024-5. doi: 10.1016/j.jaci.2015.11.023.

[69] Song WJ, Jo EJ, Lee JW, et al. *Staphylococcal enterotoxin specific IgE and asthma a systematic review and meta analysis.* Asia Pac Allergy 2013;3:120-6.

[70] Bachert C, Van Steen K, Zhang N, et al. *Specific IgE against* Staphylococcus aureus *enterotoxins: an independent risk factor for asthma.* J Allergy Clin Immunol 2012;130:376-81.e8.

[71] Kowalski ML, Cieślak M, Pérez-Novo CA, et al. *Clinical and immunological determinants of severe/refractory asthma (SRA): association with staphylococcal superantigen-specific IgE antibodies.* Allergy 2011;66:32-8.

[72] Song WJ, Sintobin I, Sohn KH, et al. *Staphylococcal enterotoxin IgE sensitization in late-onset severe eosinophilic asthma in the elderly.* Clin Exp Allergy 2016;46:411-21.

[73] Bachert C, Gevaert P, Howarth P, et al. *IgE to* Staphylococcus aureus *enterotoxins in serum is related to severity of asthma.* J Allergy Clin Immunol 2003;111:1131-2.

[74] Jing Y, Gravenstein S, Chaganty NR, et al. *Aging is associated with a rapid decline in frequency, alterations in subset composition, and enhanced Th2 response in CD1d-restricted NKT cells from human peripheral blood*. Exp Gerontol 2007;42:719-32.

[75] Pawelec G. *Immunosenescence comes of age. Symposium on Aging Research in Immunology: the impact of genomics.* EMBO reports 2007;8:220-3.

[76] Busse PJ, Mathur SK. *Age-related changes in immune function: effect on airway inflammation.* J Allergy Clin Immunol 2010;126:690-9; quiz 700-691.

[77] Pride NB, Vermeire P, Allegra L. *Diagnostic labels applied to model case histories of chronic airflow obstruction: responses to a questionnaire in 11 North American and Western European countries.* Eur Respir J 1989;2:702-9.

[78] O'Donnell DE, Aaron S, Bourbeau J, et al. *Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease 2007 update*. Can Respir J 2007;14(Suppl B):5B-32B.

[79] Miravitlles M, Soler-Cataluña JJ, Calle M, et al; Spanish Society of Pulmonology and Thoracic Surgery, Spanish Society of Pulmonology and Thoracic Surgery. *Spanish COPD Guidelines (GesEPOC): pharmacological treatment of stable COPD.* Arch Bronconeumol 2012;48:247-57.

[80] GINA-GOLD. *Diagnosis of disease of chronic airflow limitation: asthma, COPD and asthma-COPD overlap syndrome (ACOS).* http://www.goldcopd. org/asthma-copd-overlap.html.

[81] Louie S, Zeki AA, Schivo M, et al. *The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations*. Expert Rev Clin Pharmacol 2013;6:197-219

[82] De Marco R, Pesce G, Marcon A, et al. *The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle aged and elderly people from the general population.* PLoSONE 2013;8:e62985.

[83] Blanchette CM, Gutierrez B, Ory C, et al. *Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a Medicare Advantage population*. J Manag Care Pharm 2008;14:176-85.

[84] Miravitlles M, Soriano JB, Ancochea J, et al. *Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status*. Respir Med 2013;107:1053-60.

[85] Shaya FT, Dongyi D, Akazawa MO, et al. *Burden of concomitant asthma and COPD in a Medicaid population.* Chest 2008;134:14-9.

[86] Spicuzza L, Scuderi V, Morjaria JB, et al. *Airway responsiveness to adenosine after a single dose of fluticasone propionate discriminates asthma from COPD*. Pulm Pharmacol Ther 2014;27:70-5.

[87] Bousquet J, Van Cauwenberge P, Khaltaev N. *Allergic rhinitis and its impact on asthma*. J Allergy Clin Immunol 2001;108(Suppl 5):S147-334.

[88] Braunstahl GJ. *The unified immune system: respiratory tract-nasobronchial interaction mechanisms in allergic airway disease*. J Allergy Clin Immunol 2005;115:142-8.

[89] Jarvis D, Newson R, Lotvall J, et al. *Asthma in adults and its association with chronic rhinosinusitis The GALEN survey in Europe*. Allergy 2012;67:91-8.

[90] Moore WC, Bleecker ER, Curran-Everett D, et al. *Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program*. J Allergy Clin Immunol 2007;119:405-13.

[91] Vashishta R, Soler ZM, Nguyen SA, et al. *A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis*. Int Forum Allergy Rhinol 2013;3:788-94.

[92] Fass R, Pulliam G, Johnson C, et al. *Symptom severity and esophageal chemosensitivity to acid in older and young patients with gastro-esophageal reflux*. Age Ageing 2000;29:125-30.

[93] Sonnenberg A, Steinkamp U, Weise A, et al. *Salivary secretion in reflux esophagitis*. Gastroenterology 1982;83:889-95.

[94] Lackey RF. *Gastro-esophageal reflux disease and asthma*. Global Atlas of Asthma 2013.

[95] Irwin RS, French CL, Curley FJ, et al. *Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects*. Chest 2009;136:e30.

[96] Gibson PG, Henry RL, Coughlan JL. *Gastro-esophageal reflux treatment for asthma in adults and children.* Cochrane Database Syst Rev 2003;2:CD001496.

[97] Sandur V, Murugesh M, Banait V, et al. *Prevalence of gastro-esophageal reflux disease in patients with difficult to control asthma and effect of proton pump inhibitor therapy on asthma symptoms, reflux symptoms, pulmonary function and requirement for asthma medications*. J Postgrad Med 2014;60:282-6.

[98] Bixler EO, Vgontzas AN, Ten Have T, et al. *Effects of age on sleep apnea in men: I. Prevalence and severity.* Am J Respir Crit Care Med 1998;157:144-8.

[99] Teramoto S, Yamamoto H, Ouchi Y. *Increased C-reactive protein and increased plasma interleukin-6 may synergistically effect the progression of coronary atherosclerosis in obstructive sleep apnea syndrome*. Circulation 2003;107:E40.

[100] Ballard RD, Irvin CG, Martin RJ, et al. *Influence of sleep on lung volume in asthmatic patients and normal subjects.* J Appl Physiol 1990;68:2034-41.

[101] Coogan PF, Yu J, O'Connor GT, et al. *Depressive symptoms and the incidence of adult-onset asthma in African American women*. Ann Allergy Asthma Immunol 2014;112:333-8.e1.

[102] Ritz T, Claussen C, Dahme B. *Experimentally induced emotions, facial muscle activity, and respiratory resistance in asthmatic and non-asthmatic individuals*. Br J Med Psychol 2001;74:167-82.

[103] Ritz T. *Probing the psychophysiology of the airways: physical activity, experienced emotion, and facially expressed emotion*. Psychophysiology 2004;41:809-21.

[104] Wright RJ, Rodriguez M, Cohen S. *Review of psychosocial stress and asthma: an integrated biopsychosocial approach.* Thorax 1998;53:1066-74.

[105] Wright RJ. *Stress and atopic disorders*. J Allergy Clin Immunol 2005;116:1301-6.

[106] Pariante CM, Miller AH. *Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment.* Biol Psychiatry 2001;49:391-404.

[107] Sternberg EM. *Neuroendocrine regulation of autoimmune/inflammatory disease*. J Endocrinol 2001;169:429-35.

[108] Carr MC. *The emergence of the metabolic syndrome with menopause*. J Clin Endocrinol Metab 2003;88:2404-11.

[109] Atwood CS, Bowen RL. *A multi-hit endocrine model of intrinsic adult-onset asthma*. Ageing Res Rev 2008;7:114-25.

[110] Balzano G, Fuschillo S, De Angelis E, et al. *Persistent airway inflammation and high exacerbation rate in asthma that starts at menopause.* Monaldi Arch Chest Dis 2007;67:135-41.

[111] Foschino Barbaro MP, De Tullio R, Cagnazzo MG, et al. *Asthma and the menopause.* Ageing Lung 2006;1:13-9.

[112] Foschino Barbaro MP, Costa VR, Resta O, et al. *Menopausal asthma: a new biological phenotype?* Allergy 2010;65:1306-12.