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Allergic Asthma and Aging

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1. Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are the result of particular inflammatory processes that occur over time. Both of these diseases can lead to chronic obstructive airway abnormalities and contribute to a significant social and economic burden on the patient, family, and healthcare system. Distinguishing between COPD and asthma is important because the therapy and expected progression and outcomes of the two conditions are different. Respiratory disease misdiagnosis is common: up to 25% of patients over 40 years of age who are labeled as having asthma actually have COPD. Conversely, many patients in primary care are labeled as having COPD when they in fact have asthma.

Asthma in the elderly is an increasingly serious health issue. Due to the worldwide population trend to enhanced longevity, the number of elderly with asthma will rise in the coming years.

The definition of atopic conditions like asthma, is based on the ability to mount an IgE response to common allergens. Traditionally, the atopy has been associated with atopic asthma and other diseases of childhood and adolescence, which seemed less important at older ages. The allergic asthmatics, who lived through the atopic epidemic between 1970 and 1980, today are older, and now many of them are age ≥ 64 years. Entering the third millennium, physicians must embrace the new demographic challenge. Therefore the atopic diseases, as asthma, in the elderly will be an increasingly serious health issue. Physicians who treat patients with asthma are well aware that there is considerable variability in the course of the disease. Some asthmatics seem to recover completely. Others have long remissions with occasional mild relapses. Most seem to continue unchanged for many years. Asthma may persist from childhood or have its onset in adult life. The presence of atopy increases the incidence of asthma in children and young adults. This observation had promoted the concept that atopy decreases with age and hence asthma also decreases.
Elderly asthmatic patients mainly include those who have acquired the disease during childhood or adolescence and whose disease has progressed over time or is recurrent after periods of remission (elderly asthmatics, long life), but the first manifestations of asthma can occur even in late adulthood or after 65 years of age (the elderly, asthmatics, late-onset). These considerations, taken in isolation, have resulted in asthma being under-diagnosed and under-treated in elderly patients, which may be due to diagnostic misclassification. Underestimation of the prevalence of asthma may be due to confusion with COPD.

In this chapter, after describing the basics of atopy and immune alteration of the immune system in the elderly, we will examine the flow characteristics of the pathophysiology of asthma and COPD, establish the basis for correct diagnosis of asthma, highlighting the confounding factors of diagnosis, and the importance of monitoring the clinical course, identifying areas for improvement.

2. Definition of asthma

Scientific knowledge has changed the definition of bronchial asthma and is now defined as reported by the National Institutes of Health (NIH) [1]. Asthma is defined as an inflammatory disorder of the airway associated with airflow obstruction and bronchial hyper-responsiveness, This definition replaces the previous definition of asthma in which only the airflow obstruction and the bronchial hyper-responsiveness was emphasized [2].

2.1 Epidemiology

The overall prevalence of asthma in children and adults varies in European countries, with estimates of 15%–18% in the United Kingdom, 7% in France and Germany, 4.4 Italy and of 1.9 in Albania [3].

Long considered a disease of childhood or young adulthood, its prevalence is now known to be similar in older people [4].

The incidence of newly diagnosed asthma in patients ≥ 65 years is 0.1%/years in a population based study done on Rochester residents [5].

Asthma may persist from childhood or have its onset in adult life. The primary variable for persistence and severity of asthma identified in longitudinal studies is the severity in childhood. However, common sense and everyday experience tell us that continued exposure to relevant indoor allergens is also important [6,7].

The studies also suggest that sensitization and exposure to outdoor allergens, result in more persistent and severe asthma [8]. The presence of atopy increases the incidence of asthma in children and may also increase the incidence in young adults.

A cohort of college students evaluated for hay fever or asthma were followed up 23 years later. At the age of 40 years, about half of subjects who had asthma as freshmen continued to have asthma. Of these subjects, half (a quarter of the entire group) reported that they continued to have about the same frequency and severity of symptoms; very few were worse. During these 23 years, 5.2% of subjects who did not have asthma as freshmen developed asthma subsequently; the yearly incidence rate was 0.23%. The presence of positive skin test results or hay fever as freshmen did not affect the incidence of new cases of asthma as these subjects...
grew older. Unfortunately, skin tests were not performed at the 23-year follow-up of middle-aged adults, so it is not known whether these new cases of asthma were allergic [9].

The incidence of asthma is the same in patients age 65 to 84 years as it is in younger adults [10]. However, the disease may be more likely to persist and progress in severity. A cross-sectional study of 242 patients with asthma age 65 and older found that 80% had irreversible obstruction; 20% of them were unable to achieve an FEV1 greater than 50% predicted. The authors concluded that only a part of this irreversibility is the result of airway remodeling from asthmatic inflammation [10].

The diagnosis of asthma may be more difficult in the elderly because of the high prevalence of other disorders that can have similar symptoms, and because airflow obstruction is often caused by chronic obstructive pulmonary disease [11].

2.2 The problems of asthma

Under-diagnosis of asthma may occur in older people because they attribute breathlessness to normal aging and because common symptoms are often dismissed by doctors as being 'normal'. Physicians commonly underestimate the severity of breathlessness and even when breathlessness is seen as a 'problem' the possibility of asthma is often not considered [12]. The differential diagnosis of breathlessness includes not only asthma but also other conditions common in older people including chronic obstructive pulmonary disease (COPD), heart failure and obesity. Identifying the asthmatic patients from the one-third of the older population with significant breathlessness is quite a challenge [13]. A Dutch investigation has estimated that the identification of new cases of asthma or chronic obstructive pulmonary disease in an adult population subjected to a screening program cost $500–1000 per case [14].

Wheeze and sensation of bronchospasm are the symptoms which suggest the diagnosis of asthma, but they may be absent in older asthmatic patients. Furthermore, the perception of bronchoconstriction in asthmatic patients falls throughout adulthood [15]. In elderly patients there is a close relationship between the severity of wheezing complaints and impairment of the forced expiratory volume in 1 second (FEV1). Elderly patients with long-standing asthma have more severe airway obstruction than patients with recently acquired disease but patients with newly diagnosed asthma experienced a more rapid rate of decline FEV1 than patients with chronic asthma [16,17].

The asthmatic symptoms such as wheeze and sensation of bronchospasm, can have more than one cause in one elderly individual. In addition, in older patients co-morbidities may be present, such as senile dementia, which may alter the clinical presentation of asthma [18].

Several recent reviews have recommended the need for a global multidimensional assessment of obstructive airway diseases, i.e. asthma and COPD, in older people. [19,20]

3. Differential diagnosis of asthma in older patients

The differential diagnosis of asthma from other obstructive airway diseases, should include cardiac disease, tumors (laryngeal, tracheal, lung), bronchiectasis, foreign body, interstitial lung disease, pulmonary emboli, aspiration, vocal cord dysfunction, hyperventilation, anaphylactic reactions, (uncommon in the elderly unless atopic), obesity and some medications.
3.1 Obstructive airway diseases

Emphysema and chronic bronchitis are encompassed within the term COPD. COPD should be considered in any patient >35 years of age with risk factors, usually smoking, who presents with dyspnoea on exertion, chronic cough, frequent winter 'bronchitis' or wheeze. [21]. None of these symptoms are specific to COPD, and several other disorders may present with similar symptoms, signs and spirometry results, such as asthma, bronchiectasis, congestive cardiac failure and carcinoma of the bronchus. COPD is defined by the presence of airflow limitation that is “not fully reversible and does not change markedly over several months” [21]. Traditionally measurement of the degree of reversibility using bronchodilators or corticosteroids has been used to confirm the diagnosis and in particular to try to separate patients with asthma from those with COPD [22]. However, the same study in patients with fixed airflow obstruction diagnosed as having COPD, on the basis of the clinical history has shown that the clinical diagnosis was correct as assessed by the basis of the pattern of inflammation seen on the differential cell counts in induced sputum findings. Reversibility testing was unable to differentiate patients with COPD from patients with asthma [22].

3.2 Left ventricular failure

Left ventricular failure (LVF) can sometimes be very difficult to differentiate from asthma as signs can be unreliable in older people. The following characteristics are present both in LVF and in asthma: airways obstruction, bronchial hyper-reactivity and episodic nocturnal dyspnoea. A history of ischemic heart disease is suggestive of heart failure, but not necessarily so, as diseases can co-exist [23].

Levels of B-type natriuretic peptide (BNP), a neurohormone secreted by the left ventricle in response to volume-elevated left ventricular pressure, are higher in acute and chronic heart failure. Measurement of plasma BNP proved to be a useful diagnostic test in differentiating HF from other causes in patients who presented with dyspnea [24].

3.3 Gastro-esophageal reflux disease (GERD)

The incidence of gastro-esophageal reflux disease (GERD) increases with age and leads to broncho-constriction via microaspiration and vagal stimulation. Methylxanthines used to treat asthma can reduce lower esophageal pressure and cause aspiration. GERD should be considered in elderly patients with heartburn or nocturnal symptoms occurring early at night [25].

3.4 Aspiration

Conditions resulting in reduced conscious level, such as dementia, Parkinson's disease and stroke as well as use of medications such as sedatives, alcohol and antipsychotics, and immobility increase the risk of aspiration [26].

3.5 Tumors (laryngeal, tracheal, lung)

Tumors that affect the central airways, i.e. cancers of tracheal or of the proximal bronchus, and the bronchogenic carcinoma, or mediastinal lymphadenopathy may present with
cough, wheeze and dyspnoea, all symptoms of asthma. Also the gastric and breast cancer spread via lymphatics and can produce wheeze [27,28].

3.6 Pulmonary embolism (PE)
In PE breathless and tachypnoeic (> 20 breaths/min) are the most prominent signs, while bronchoconstriction is less often present. Differentiating asthma from PE, in the absence of pleuritic chest pain, is very difficult. However, computed tomographic pulmonary angiography is usually recommended for the diagnosis of PE [29]. A blood D-dimer test can be useful [30].

3.7 Drugs
Polypharmacy is common in outpatients and has been identified as a major risk factor for drug-drug interactions (DDIs), which are an important cause of adverse drug reactions [31]. Therefore a detailed drug history is essential. β-adrenoceptor antagonist drugs [32], aspirin and NSAIDs, may worsen asthma control by inducing bronchospasm[33]. ACE inhibitors can cause cough [34]. Methylxanthines can reduce lower esophageal sphincter tone, increase GERD and cause ’uncontrolled’ asthma [35].

4. Definition of Chronic obstructive pulmonary disease
Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. The more familiar terms ‘chronic bronchitis’ and ‘emphysema’ are no longer used, but are now included within the COPD diagnosis [36].

While asthma features obstruction to the flow of air out of the lungs, usually, the obstruction is reversible. Between "attacks" of asthma the flow of air through the airways typically is normal. These patients do not have COPD. However, if asthma is left untreated, the chronic inflammation associated with this disease can cause the airway obstruction to become fixed. That is, between attacks, the asthmatic patient may then have abnormal air flow. This process is referred to as lung remodeling. These asthma patients with a fixed component of airway obstruction are also considered as having COPD [22].

Often patients with COPD are labeled by the symptoms they are having at the time as an exacerbation of their disease. For instance, if they present with mostly shortness of breath, they may be referred to as emphysema patients. While if they have mostly cough and mucus production, they are referred to as having chronic bronchitis. In reality, it is better to refer to these patients as having COPD since they can present with a variety of lung symptoms. There is frequent overlap among COPD patients. Thus, patients with emphysema may have some of the characteristics of chronic bronchitis and vice a versa [37].

4.1 Causes of COPD
4.1.1 Smoking
Smoking is responsible for 90% of COPD [36]. Although not all cigarette smokers will develop COPD, it is estimated that 15% will. Smokers with COPD have higher death rates
than nonsmokers with COPD [38]. They also have more frequent respiratory symptoms (coughing, shortness of breath, etc.) and more rapid deterioration in lung function than non-smokers [36]. It is important to note that when COPD patients stop smoking, their decline in lung function slows to the same rate as nonsmokers [36,39]. Therefore, it is never "too late" to quit.

Effects of passive smoking or "second-hand smoke" on the lungs are not well understood; however, evidence suggests that respiratory infections, asthma, and symptoms are more common in children who live in households where adults smoke [2]. Cigarette smoking damages the lungs in many ways. For example, the irritating effect of cigarette smoke attracts cells to the lungs that promote inflammation. Cigarette smoke also stimulates these inflammatory cells, predominantly neutrophils, to release elastase, an enzyme that breaks down all components of the extracellular matrix including the elastic fibers in lung tissue [40].

4.1.2 Air pollution

Air pollution can cause problems for persons with lung disease, but it is unclear whether outdoor air pollution contributes to the development of COPD. However, in the non-industrialized world, the most common cause of COPD is indoor air pollution. This is usually due to indoor stoves used for cooking [41,42].

4.1.3 Occupational pollutants

Some occupational pollutants such as silica and cadmium do increase the risk of COPD. Persons at risk for this type of occupational pollution include coal miners, construction workers, metal workers, cotton workers, etc. Most of this risk is associated with cigarette smoking and these occupations, an issue not well controlled for. These occupations are more often associated with the pneumoconioses than are the interstitial lung diseases. Nevertheless, the adverse effects of smoking cigarettes on lung function are far greater than occupational exposure [43].

4.1.4 Alpha-1 antitrypsin

Another well-established cause of COPD is a deficiency of alpha-1 antitrypsin (AAT). AAT deficiency is a rare genetic (inherited) disorder that accounts for less than 1% of the COPD in the United States.

Normal function of the lung is dependent on elastic fibers surrounding the airways and in the alveolar walls. Elastic fibers are composed of a protein called elastin. An enzyme called neutrophil elastase that is found even in normal lungs (and is higher in cigarette smokers) can break down the elastin and damage the airways and alveoli. Another protein called alpha-1 antitrypsin (AAT) (produced by the liver and released into the blood) is present in normal lungs and can block the damaging effects of elastase on elastin. It does this on a one molecular basis, so that one molecule of AAT inhibits one molecule of neutrophil elastase, preventing elastase related destruction of surrounding tissue (proteolysis).

The manufacture of AAT by the liver is controlled by genes which are contained in DNA-containing chromosomes that are inherited. Each person has two AAT genes, one inherited
from each parent. There are multiple inherited single nucleotide polymorphisms which alter the tertiary structure of the AAT protein, and can alter its release from liver cells (causing liver damage in some cases, and can alter the levels of AAT in blood. Individuals who inherit two copies of the most defective AAT polymorphism (PiZ) (one from each parent) have both low amounts of AAT in the blood and AAT that does not function properly as it forms strings of joined proteins (polymers) which cannot inhibit elastase and are pro-inflammatory in their own right. The reduced action of AAT in these individuals allows the destruction of tissue in the lungs by elastase to continue unopposed. This causes emphysema by age 30 or 40. Cigarette smoking accelerates the destruction and results in an even earlier onset of COPD.

Individuals with one normal and one defective AAT gene have AAT levels that are lower than normal but higher than individuals with two defective genes. These individuals may have an increased risk of developing COPD if they do not smoke cigarettes; however, their risk of COPD probably is higher than normal if they smoke. Though their Alpha-1 antitrypsin blood levels may be in the normal range, the function of this enzyme is impaired relative to normal patients. Some may even develop bronchiectasis instead of emphysema.

5. Symptoms of COPD

Typically, after smoking 20 or more cigarettes a day for more than twenty years, patients with COPD develop a chronic cough, shortness of breath (dyspnea), and frequent respiratory infections [36]. In patients affected predominantly by emphysema, shortness of breath may be the major symptom. Dyspnea usually is most noticeable during increased physical activity, but as emphysema progresses, dyspnea occurs at rest. In patients with chronic bronchitis as well as bronchiectasis, chronic cough and sputum production are the major symptoms [46]. The sputum is usually clear and thick. Periodic chest infections can cause fever, dyspnea, coughing, production of purulent (cloudy and discolored) sputum and wheezing. (Wheezing is a high pitched noise produced in the lungs during exhalation when mucous, bronchospasm, or loss of lung elasticity obstructs airways.) Infections occur more frequently as bronchitis and bronchiectasis progress.

In advanced COPD, patients may develop cyanosis (bluish discoloration of the lips and nail beds) due to a lack of oxygen in blood. They also may develop morning headaches due to an inability to remove carbon dioxide from the blood. Weight loss occurs in some patients, due to combination of reduced intake of food, the additional energy that is required to breathe and the cachectic consequences of inflammation, in particular excessive Tumor Necrosis Factor alpha (TNFα) acting via leptin. In advanced COPD, small blood vessels in the lungs are destroyed, and this blocks the flow of blood through the lungs. As a result, the heart must pump with increased force and pressure to get blood to flow through the lungs. The elevated pressure in the blood vessels of the lungs develops pulmonary hypertension. If the heart cannot manage the additional work, right heart failure also known as Cor pulmonale results and leads to swelling of the feet and ankles.

Patients with COPD may cough up blood (hemoptysis). Usually hemoptysis is due to damage to the inner lining of the airways and the airways’ blood vessels; however, occasionally, hemoptysis may signal the development of lung cancer [47,48].
6. Diagnosis of COPD

COPD is usually diagnosed on the basis of a medical history, the symptoms of COPD and the physical examination which reveals signs of COPD [22, 49]. The tests to diagnose COPD include tests of lung function (spirometry), the measurement of carbon dioxide, oxygen levels in the blood, chest X-ray and computerized tomography (CT) scan of the chest. The medical history of patients with COPD is often suspected in chronic smokers who develop shortness of breath with or without exertion [22, 36]. These patients have chronic persistent cough with sputum production, and frequent infections of the lungs. Sometimes COPD is first diagnosed after a patient develops a respiratory illness necessitating hospitalization. Some physical findings of COPD include enlarged chest cavity and wheezing. Faint and distant breath sounds are heard when listening to the chest with a stethoscope. Air is trapped in the lungs from the patient's inability to empty their lungs with exhalation. This extra air dampens the sounds heard and results in the overinflated chest cavity. In patients affected predominantly with emphysema, the chest X-ray may show an enlarged chest cavity and decreased lung markings reflecting destruction of lung tissue and enlargement of air-spaces. In patients with predominantly chronic bronchitis, the chest X-ray may show increased lung markings which represent the thickened, inflamed and scarred airways. CT scans of the chest show the abnormal lung tissue and airways in COPD. Chest X-rays and CT scans of the chest are also useful in excluding lung infections (pneumonia) and cancers. CT of the chest usually is not necessary for the routine diagnosis and management of COPD, but can be helpful in evaluating the extent of emphysematous change as well as detecting early lung cancers [36].

Spirometry is a test which quantitates the amount of airway obstruction and its reversibility after bronchodilator. Oxygen and carbon dioxide levels are measured in samples of arterial blood. A noninvasive method to measure oxygen levels in the blood is the pulse oximetry. Another very effective and simple test used to monitor COPD is called the six minute walking test (6MWT) [50]. The patient is asked to walk on a level surface at their own pace for six minutes. There is a very detailed script that is utilized when performing this test. The patient is informed about the time left to complete the test, but no encouragement is offered. The patient may stop and rest at any time during the study. The distance traveled is measured and is a very accurate index of the state of health and effectiveness of therapy.

7. Differences between asthma and COPD

Asthma and COPD are very different in terms of cellular mechanisms, inflammatory mediators, inflammatory effects, and response to therapy. Both diseases are characterized by airflow obstruction and a chronic persistent inflammatory process, but the nature of the inflammation differs markedly between these diseases [51, 52].

7.1 Inflammatory cells

Airway inflammation in asthma is characterized by an eosinophilic inflammation, with an increase in activated and degranulating eosinophils in bronchial biopsies, BAL, and in induced sputum [22, 53]. There is also an increase in CD4 T lymphocytes (T-helper type 2 cells) that appear to orchestrate the eosinophilic inflammation and degranulated mast cells that underlie the rapid and episodic bronchoconstrictor responses that are so characteristic
of asthma. Airway inflammation in asthma is characterized by an eosinophilic inflammation, with an increase in activated and degranulating eosinophils in bronchial biopsies, BAL, and in induced sputum [54]. Epithelial shedding is a common feature of biopsies from asthmatic airways and may be a consequence of eosinophilic inflammation. Inflammation affects all of the airways in asthma and does not involve the lung parenchyma. Fibrosis is remarkable by its absence, and although much has been made of the subepithelial fibrosis, this is trivial in amount and is seen even in patients with very mild asthma of short duration. Airway hyper-responsiveness is the characteristic physiological abnormality in asthma, and although its mechanism is uncertain, it is linked to eosinophilic inflammation [54].

The pathology of COPD differs clearly from that of asthma [55]. In larger airways, there is evidence of neutrophil rather than an eosinophilic inflammation, as judged by increased numbers of neutrophils in BAL [54,55]. Induced sputum shows a characteristic increase in the proportion of neutrophils that is much greater in patients with COPD than in smokers without obstruction. Granulocyte markers of neutrophil inflammation, namely myeloperoxidase and human neutrophil lectin, are actively degranulating [56]. The eosinophils can be present in the induced sputum of patients with COPD. However, the eosinophils aren’t activated [22]. The neutrophils transit rapidly from the circulation into the airway lumen, as demonstrated by the bronchial biopsies that have demonstrated an infiltration with mononuclear cells, CD8+ T lymphocytes, rather than neutrophils. A similar inflammatory aspect has been shown in bronchial biopsies of ex-smokers, confirming that inflammation may persist in the airway once established [57].

In the lung parenchyma a predominance of macrophages and CD8+ T cells have been found at sites of parenchymal destruction [53, 55, 57]. Finally in COPD, a squamous metaplasia can be present. In contrast to asthma, most of the pathologic changes are found in peripheral airways, where there is also fibrosis, resulting in an obliteratorive bronchiolitis [53].

In patients with COPD the airway hyper-responsiveness is not a common feature. Furthermore, in COPD, unlike asthma, patients do not constrict with indirect bronchial challenges, such as exercise [55].

Cigarette smoking and/or other inhaled irritants may initiate an inflammatory response in the peripheral airways and lung parenchyma. It is likely that neutrophil chemotactic factors are released from activated macrophages and also from epithelial cells and CD8+ T lymphocytes [53, 57].

Although both COPD and asthma involve chronic inflammation of the respiratory tract, the pattern of inflammation is markedly different between these two diseases (Table 1). Mild asthma is characterized by eosinophilic inflammation driven by TH2 cells and DCs, and is associated with mast-cell sensitization by IgE, and by the release of multiple bronchoconstrictors. By contrast, COPD is characterized by neutrophilic inflammation that can be driven by a marked increase in the number of lung-resident macrophages, which also attract CD4+ and CD8+ T cells to the lungs. This lymphocytic infiltration can also be driven by chronic stimulation by viral and bacterial antigens or by autoantigens released following lung injury. Mast cells and DCs, which have such a key role in asthma, have little or no known involvement in COPD. However, these distinctions between asthma and COPD may not be as clear as previously believed, as in patients with severe asthma and in asthmatic
individuals who smoke there is a neutrophilic pattern of inflammation, and acute exacerbations of asthma and of COPD have similar inflammatory features [54]

<table>
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<th></th>
<th>Mild</th>
<th>Asthma</th>
<th>Severe</th>
<th>Exacerbation</th>
<th>Mild</th>
<th>COPD</th>
<th>Severe</th>
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<td>++++</td>
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<td>Th6 cells +</td>
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<td>IL13 ++, CCL11+</td>
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0 = no response; + to ++++, magnitude response; ? = uncertain

Table 1. The pattern of inflammation and the response to steroid in asthma and COPD

7.2 Inflammatory mediators

More than 50 inflammatory mediators have been found in asthma [58]. In table 1 we reported the cells and mediators that characterized asthma and COPD. Histamine, prostaglandin and kinins derive from mast cells and basophils. Cysteinyl-leukotrienes derive from mast cells and eosinophils. These inflammatory mediators, particularly kinins, could activate the cholinergic reflex. In contrast, there are likely to be few bronchoconstrictor mediators released in COPD airways, and cholinergic tone is likely to be the only reversible component. This explains why anticholinergic drugs are relatively more effective in COPD and may be even more effective than β2-agonists [58].

In induced sputum of patients with COPD elevated levels of Leukotriene-B4 (LTB4) have been found, which it is a potent neutrophil chemoattractant [59]. The cytokines of asthma: interleukin (IL)-4 and IL-13, are likely to be important, as they are necessary for IgE formation, whereas IL-5 is critical for eosinophilic inflammation [60].

Eosinophil chemotactic cytokines (CC chemokines), such as eotaxin and RANTES, are also important in asthmatic inflammation and selectively recruit primed eosinophils from the circulation into the airways [58].

IL-8 is a selective attractant of neutrophils and its levels in induced sputum are correlated with the extent of neutrophilic inflammation and with disease severity (% predicted FEV1) of COPD [56, 59] Other CXC chemokines, such as GRO-α, may also be involved in neutrophil recruitment in COPD. Also, Tumor necrosis factor-α is present in high concentration in the sputum of COPD patients, and may activate the transcription of nuclear factor-kB which switches on the transcription of the IL-8 gene [61].

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Markers of oxidative stress are higher in COPD. This is likely to be because of the large increase in activated macrophages and neutrophils in COPD, and the effects of cigarettes, which provide high oxidative stress [62].

7.3 Enzymes

The predominant inflammatory enzyme involved in asthma is the tryptase that is produced by the mast cell. Tryptase plays an important role in AHR and in some aspects of airway remodeling in asthma [63].

COPD proteinase/antiproteinase imbalance

Excessive activity of proteases, and an imbalance between proteases and endogenous antiproteases is the characteristic of COPD.

The destruction of lung parenchymal is due to several proteases. Neutrophil elastase, a neutral serine protease, is the major constituent of lung elastolytic activity and also potently stimulates mucus secretion [64]. In the patient’s α1-antitrypsin deficiency this enzyme activity is likely to be the major mechanism mediating elastolysis, and may not be the major elastolytic enzyme in smoking-related COPD [65]. It is important to consider other enzymes as targets for inhibition, including cathepsins, collagenase (MMP-1), gelatinase B (MMP-9) and matrix metalloproteinases (MMPs). MMPs are produced by several inflammatory cells, including macrophages and neutrophils [65]. Some metalloproteinases, MMP-2 and MMP-9, have been found in the parenchyma of patients with emphysema. The levels of MMPs are lower in patients with asthma and may be derived predominantly from eosinophils; this is not surprising since parenchymal destruction is not a feature of asthma [66]. CD8+ (cytotoxic or Tc cells) may also contribute to parenchymal destruction through the release of proteolytic perforins and granzymes.

COPD oxidant/antioxidant imbalance

The lung is susceptible to oxidative injury by virtue of myriads of reactive forms of oxygen species and free radicals. Reactive oxygen species and reactive nitrogen species are highly unstable due to unpaired electrons that are capable of initiating oxidation. As a part of their normal physiology and external challenges posed by various microorganisms and chemicals, biological systems continuously generate reactive oxygen/nitrogen species to ward off these agents and in turn are exposed to the deleterious effects of these reactive species. Free radical species may be endogenously produced by metabolic reactions (e.g. from mitochondrial electron transport during respiration or during activation of phagocytes) or exogenously, such as air pollutants or cigarette smoke [67]. Antioxidants are major in vivo and in situ defence mechanisms of the cells against oxidative stress. Two classes of antioxidants are recognized: (a) non-enzymatic antioxidants such as Vitamins E, Vitamin C, β-carotene, GSH and (b) enzymatic antioxidants such as GSH redox system comprising of glutamate cysteine ligase, glutathione reductase, glutathione peroxidase, glucose-6-phosphate dehydrogenase, and in addition superoxide dismutases, catalase, heme oxygenase-1, peroxiredoxins, thioredoxins and glutaredoxins. The two classes of antioxidants often work in tandem with each other and are involved in redox recycling process. The human lungs and different inflammatory cells exhibit diverse antioxidant profiles. Depending on the status of the antioxidants in a particular region and the specific burden, a specific disease process may be initiated. All the major varieties of inflammatory
lungs, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, interstitial lung diseases and bronchopulmonary dysplasia share a common feature of impaired oxidant/antioxidant ratio. The localization of specific antioxidant enzymes in various sub-compartments of lung tissue, particularly during lung diseases remains largely unclear. It may be possible that various antioxidant enzymes are expressed in a cell-specific manner depending upon the milieu of deleterious reactive oxygen species generated. Emerging data indicate that various antioxidant enzymes are upregulated at the level of mRNA expression but actually have low enzyme activity or low levels of proteins [68].

8. Immune-senescence and asthma

The last clinical manifestation of asthma is generally considered the arrival of atopic march. The atopic march is generally characterized by the progression of atopic dermatitis to asthma and allergic rhinitis during the first years of life. The putative mechanism is the skin, which acts as the site of primary sensitization through possible defects in the epidermal barrier with later sensitization in the airways [69].

The typical inflammation of allergic asthma and other allergic diseases, as allergic rhinitis, consists of predominantly Th2 lymphocytes and cytokines, e.g. IL-4, IL-5, and IL-13 [54]. Studies of induced sputum, bronchoalveolar fluid, and bronchial biopsies have shown an inflammation that consists of T-cells and eosinophils. In addition to these cells, the expression of a number of inflammatory mediators including cytokines, chemokines, and lipids (prostaglandins and leukotrienes) are significantly higher in the airway, see paragraph 6.0 Differences between asthma and COPD [58]. The IL-13 and leukotriene LTC4 can directly induce the pathophysiological hallmarks of asthma, including airway hyper-responsiveness, goblet cell hyperplasia, mucus secretion, and smooth muscle cell hypertrophy [72,73]. It is recognized as a more severe asthma phenotype with a greater degree of airflow obstruction, more frequent exacerbations, and a greater rate of lung function decline. In a study comparing patients with asthma of long duration and patients with asthma of short duration, it was found that the duration of asthma is associated with the degree of airflow limitation [4].

An important “trigger” of asthma exacerbations is upper respiratory tract viral infection. Estimates suggest that up to 80% of asthma exacerbations in adults are caused by viral upper respiratory infections [74]. Because immune function is important for the resolution of respiratory infections, question arise regarding the impact of immune-senescence on the clinical features of asthma in the elderly [75].

Numerous studies suggest that immune function declines with aging, a phenomenon frequently referred to as “immunosenescence” [76]. This is thought to contribute to more frequent infections [77], an increased incidence of autoimmune disease [78], and increased incidence of malignancy due to impaired immune surveillance [79]. Immunosenescence has been described for both adaptive and innate components of the immune response.

The most extensively studied component of the immune system with regard to immunosenescence is the T-cell population. The involution of the thymus gland begins shortly after birth and undergoes replacement by fatty tissue that is nearly complete by 60 years of age. Consequently, a decline in the numbers of circulating naïve T-cells gradually
Allergic Asthma and Aging

occurs, and memory T-cells (CD45RO+) eventually predominate [80]. Additionally, the T-cell receptor repertoire diversity appears to diminish, and T helper cell activity declines [81]. Other observations of the T-cell population with aging include reduced proliferative responses [82], a shift of Th1 to Th2 cytokine profiles upon stimulation with PHA (phytohaemoagglutinin) [83,84] and a decline in Fas-mediated T-cell apoptosis [85]. Whether any of these age-related changes is more or less pronounced in specific inflammatory disorders, such as allergic diseases or asthma, is not known.

Also a decreased production of B-cells with aging has been observed. More specifically, there is a transition from the presence of naïve B-cells to “antigen-experienced” B-cells [86]. In addition, the quality of antibody produced is altered with lower affinity and avidity for antigen [87, 88]. The ability of neutrophils to kill phagocytosed organisms is diminished in the elderly compared to younger individuals [89].

We studied the superoxide production, chemotaxis and the expression of the apoptosis-related molecule APO1/Fas (CD95) on neutrophils (PMN) from young and old subjects. We have also measured the basal natural killer (NK) activity of young and elderly subjects comparing the number of CD16+ cells as well. We observed a significant age-related decrease both of formation of O$_2^-$ and chemotaxis, whereas no significant correlation between age and the expression of CD95 on granulocyte membrane was demonstrated, suggesting that an age-related increase of CD95-linked apoptosis of PMN should not be an important determinant in the decreased PMN function. We also observed a significant correlation between age and NK activity. The decreased NK cell function was not due to a decreased number of NK cells in effector cell preparations since the number of CD16+ cells was significantly higher in old subjects [89].

In a study examining age-related changes in eosinophil function, it was found that peripheral blood eosinophils from older asthma subjects exhibited decreased degranulation in response to cytokine stimulation and displayed a trend for decreased superoxide production [90]. However, eosinophils may have an altered or diminished role in the airway inflammation of older asthma patients and the production of IL-5 is not defective in old subjects [22, 90]. These observations strengthen the suggestions of the existence of Th-2 shift in elderly [91-93].

9. Treatment of asthma in older patients

We performed computer-assisted searches of the medical literature to identify information on the treatment of asthma in individuals over 65 years old. We reviewed the articles identified as matches for our search criteria and tabulated the data from them. We searched the PubMed/MEDLINE databases, and included citations from 1966 to 2010. Our search strategy combined medical subject headings or the text words for asthma, humans, English, aged (65+ years) and treatment.

As regards the treatment in older asthmatics using all databases, we found 2 controlled studies that focused exclusively on asthma in patients aged over 65 years: 1 on a β2-agonist and the other on a leukotriene receptor antagonist [94,95]. In the other published randomized, controlled treatment trials of asthma, the numbers of individuals aged over 65 years were small. Finally the diagnosis of asthma was approximate, many patients included were patients with both asthma and COPD. Thus, the information to follow was, for the most part, derived from less rigorous data, in part to the systematic exclusion of the elderly from clinical trials of asthma therapy [96]. However, only in 2007 in the Expert Panel Report
a section, “Special Issues for Older Adults,” specifically addressed asthma in seniors [2]. Because of the high prevalence of chronic bronchitis and emphysema among the elderly, a 2- to 3-week trial of systemic corticosteroids was suggested to detect “significant reversibility of airway disease” in patients thought to have asthma who fail to demonstrate reversibility on pulmonary function testing [22]. Because seniors have decreased awareness of bronchoconstriction, decreased physiologic responses to hypoxemia and hypercapnia, and more advanced airway obstruction than younger asthmatic patients, pulmonary function testing could be more appropriate to use than symptoms as the primary guide for treatment [4, 22]. The lack of an evidence-based approach to asthma in the elderly was attributed in part to the systematic exclusion of the elderly from clinical trials of asthma therapy [97]. Therefore the therapeutic approach to asthma in older patients does not differ from what is recommended for young patients. Treatment protocols use step-care pharmacologic therapy based on the asthma symptoms and the clinical response to these interventions. As symptoms and lung function worsen, step-up or add-on therapy is given. As symptoms improve, therapy can be “stepped down.” Several factors must be taken into consideration when considering appropriate pharmacological therapy in older patients who have asthma and special attention should also be given to the potential adverse effects of commonly used medications [98].

9.1 Anti-inflammatory

9.1.1 Corticosteroids

Because asthma is an inflammatory disease any patients with persistent asthma should receive daily anti-inflammatory therapy to control and suppress the airway inflammation [2]. The anti-inflammatory therapy of asthma is the corticosteroids [2, 99]. They have been used by Boardley et al. at Johns Hopkins University, in 1949 in patients with asthma, demonstrating good results. Subsequently, oral cortisone, widely used at that time to treat several inflammatory diseases, was shown to be an effective replacement for the injections, in patients with difficult-to-control asthma. In 1956, the first multicenter trial of cortisone placebo-controlled trial in asthma patients was done. The results of this trial were disappointing compared to Boardley’s data. However, the reasons can be traced to the low dose of cortisone used, the lack of objective measurements of lung function and the inclusion of many patients who had COPD [100,101]. However, despite this poor result, oral steroids were used in patients with severe asthma, but it was clear that side effects, stunting of growth in children, osteoporosis and metabolic disturbances, were a major problem of this treatment. A way of reducing systemic side effects was to give corticosteroids by inhalation. The first two molecules of inhalator corticosteroids used were cortisone and dexamethasone. Beclometasone dipropionate (BDP) was used successfully.

Inhaled BDP was very effective in reducing the need for oral corticosteroids and in many patients achieved better control. The authors observed that the patients who did best had high numbers of eosinophils in their sputum [102]. This observation has been confirmed in other subsequent studies and the use of inhaled corticosteroids in asthma has been the major reason why asthma morbidity and mortality have fallen [103]. There is now a search for inhaled corticosteroids with improved therapeutic ratios and less systemic side effects.
The newer inhaled corticosteroids i.e. budesonide, fluticasone propionate and mometasone furoate, have improved therapeutic ratios and less systemic side effects, because oral bioavailability has been reduced [104-106]. The last inhaled corticosteroid is the cliclosonide, which is a prodrug, activated by esterases in the lower airways [107].

There has recently been a much better understanding of the molecular mechanisms involved in the anti-inflammatory effects of corticosteroids in asthma, with particular emphasis on the effects of corticosteroids on chromatin remodeling through increased recruitment of histone deacetylase-2 to activated inflammatory genes [108, 109].

Does the prescribing of ICS to older patients increase the risk of bone fractures? A study of patients aged 56-91 years demonstrated that women who took ICS had a modest decrease in BMD compared to women who did not take corticosteroids [110]. A retrospective evaluation of 800,000 women aged >66 years found that systemic, but not inhaled, corticosteroids were associated with an increased risk of hip fractures [111]. Finally it has been demonstrated that long-term use of inhaled and nasal corticosteroids at the usual recommended doses is not associated with a risk of fracture in older patients with respiratory disease [112]. Budesonide, fluticasone propionate and mometasone have <1% oral bioavailability, whereas the oral bioavailability of beclometasone, triamcinolone and flunisolide is >10% [113]. The role of bisphosphonates in preventing fractures in patients taking ICS is controversial and studies have reported mixed results [114-115]. Observational studies in the elderly have suggested that use of ICS is associated with a small but significant risk of subcapsular and nuclear cataracts [116, 117] and development of glaucoma [118, 119]. However no randomized controlled trials have been performed to establish these aspects.

9.1.2 Chromones

Chromones are extracted from the medicinal plant Amni visnaga. The researchers of Fisons Pharmaceuticals identified the most active compounds, leading eventually to the synthesis of a bischromone, disodium cromoglycate (DSCG). DSCG was orally inactive and had to be given by a dry powder inhaler device. This drug inhibited not only antigen challenge but also challenges due to exercise and irritant gases. However, DSCG had a short duration of action, prompting the search for compounds of longer duration or that were orally active. Nedocromil sodium was introduced as a slightly longer-acting inhaled chromone but had little advantage over DSCG. Chromones have now largely been replaced by inhaled corticosteroids [120, 121].

9.2 Bronchodilating medications

9.2.1 Muscarinic receptor antagonist

Jimson weed or thorn apple, which were smoked in India for several centuries as a treatment for respiratory disorders (including asthma), contain a muscarinic receptor antagonist, atropine. The Egyptians also inhaled the vapour of heated henbane alkaloid, scopolamine, for the treatment of asthma-like conditions. These therapies were available until well into the last century. An important advance in the use of muscarinic receptor antagonists for asthma was the development of quaternary ammonium derivatives, which did not pass the blood–brain barrier and thus were devoid of the central side effects, such as...
hallucinations, of naturally occurring atropine-like compounds. They are effective when inhaled and ipratropium bromide, a synthetic quaternary antimuscarinic compound, is still used as a bronchodilator in patients with severe asthma.

The antimuscarinic agents have turned out to be the bronchodilators of choice in the treatment of COPD, where the only reversible component appears to be cholinergic tone in the airways. The recognition of distinct muscarinic receptor subtypes, which have different functions and distribution, has been a turning point. The recognition is that M3 receptors mediate the bronchoconstrictor effect of cholinergic tone, whereas M2 receptors function as feedback inhibitory receptors (autoreceptors) in human airways [122]. The clinical consequence is that the nonselective muscarinic antagonists, such as atropine and ipratropium, will also increase acetylcholine production from cholinergic nerves by blocking the M2 autoreceptors and may thus overcome the blockade of the M3 receptors on airway smooth muscle cells. This led to the idea that M3-selective antagonists may be more effective as bronchodilators. Indeed, tiotropium has a kinetic selectivity for M3 receptors as it dissociates much more slowly from M3 receptors than from M2 receptors. New developments include more long-acting muscarinic antagonists which will be used alone and in combination with long-acting β2-agonists, mainly for COPD patients [123]. Glycopyrrolate, used for many years by anesthetists to dry upper airway secretions, has recently been found to have pharmacological properties similar to tiotropium, with kinetic selectivity for M3 receptors and a long duration of action when given by inhalation [124]. One report has suggested that the use of ipratropium bromide in elderly asthmatics was associated with a slight increase in mortality, a finding that the investigators concluded was secondary to these patients having more severe asthma compared to those patients not receiving ipratropium bromide [125]. However, anticholinergics, because of their atropine-like effects may produce adverse effects in the elderly, including dry mouth, urinary hesitancy, constipation and exacerbation of glaucoma [126].

9.2.2 β2-agonist

Chinese medicine used a derivative of the Ephedra plant, ephedrine. In 1969 ephedrine was tested in humans [127]. Isoetharine, like isoprenaline was short-lived in its effects, due to rapid metabolism of the catechol ring [127]. In 1968, the first β2-selective agonist with a longer duration of action than isoprenaline was discovered: salbutamol [128]. Since then, salbutamol has been a reference molecule in the treatment of asthma [129]. The next step was to extend the duration of action of salbutamol by substitution in the side chain and the result was salmeterol, the first long-acting β2-agonist with a bronchodilator action of over 12h [130]. Inhaled salmeterol was introduced into clinical practice in 1990. Another long-acting β2-agonist, formoterol, was initially used in tablet form in Japan. Later formoterol was given by inhalation to asthmatic patients and shown to have a similar duration of action to salmeterol [131]. Both salmeterol and formoterol have found an important place in the management of asthma in combination with a corticosteroid. The combination inhalers, salbutamol/fluticasone propionate and formoterol/budesonide, and recently formoterol/beclometasone dipropionate are the most effective asthma therapies currently available, as the long-acting β2-agonist and corticosteroids exert complementary actions and, in some situations, can show synergism [132].

The most recent development being the synthesis of even longer acting β2-agonists, such as indacaterol, which has a duration of over 24h making it suitable for once-daily dosing [133].
9.2.3 Theophylline

A methyl xanthine, theophylline, was isolated from tea at the end of the 19th century. It had bronchodilator effect as reported by Hirsch [134]. Aminophylline is a soluble ethylene diamine salt of theophylline, which can be administered for intravenous and was shown to be very effective in acute severe asthma, particularly in patients who had not responded well to adrenaline [134].

Intravenous aminophylline remained a standard treatment for acute exacerbations of asthma until displaced by nebulised β2-agonists over the last 20 years. It is still used in occasional patients who fail to respond to adrenergic bronchodilators [35]. The main limitations of theophylline are its side effects, such as nausea, headache and diuresis, which occurred within the therapeutic range and occasionally the very serious adverse effects of cardiac arrhythmias and seizures.

This led to several studies relating the efficacy and side effects of theophylline to plasma concentrations. It has been demonstrated that the bronchodilator effect of theophylline was related to plasma concentration between 5 and 20 μg/mL, but above 20 μg/mL, and side effects were very common. This led to recommendations for a therapeutic range of 10–20 μg/mL. Plasma monitoring became routine, particularly in view of the variable pharmacokinetics of theophylline and the multiplicity of factors that affected plasma concentrations. Oral theophylline was a very popular treatment which was inexpensive, but presented the limitation of a short duration of action. This limitation led to the formulation of slow-release theophylline and aminophylline preparations that could be given once or twice daily, which were successful due to their convenience and greater tolerability.

Side effects limited the use of theophylline as a bronchodilator, and inhaled β2-agonists were introduced as bronchodilators that are more effective and better tolerated. The bronchodilator effect of theophylline appears to be due to inhibition of phosphodiesterases (principally PDE3 and PDE4) in airway smooth muscle and this may also account for the nausea, headaches and some of the cardiovascular side effects, explaining why these side effects are commonly seen at bronchodilator doses. Theophylline acts as a functional antagonist in airway smooth muscle and has greater efficacy than β2-agonists when airway smooth muscle is strongly contracted [135]. Theophylline is also an adenosine receptor antagonist at relatively high concentrations and this may account for serious side effects such as cardiac arrhythmias and seizures. However, there is increasing evidence that at lower plasma concentrations (5–10 μg/mL) theophylline has nonbronchodilator effects that include anti-inflammatory actions and immunomodulatory effects. These effects seem to correlate to activate the nuclear enzyme histone deacetylase [136].

9.2.4 Antagonists of inflammatory mediators

There are many mediators implicated in asthma, making it unlikely that blocking a single mediator would have a major clinical effect. Histamine is the first mediator implicated in the pathophysiology of asthma. However, it has been demonstrated that intravenous and inhaled histamine caused bronchoconstriction only in patients with asthma but not in normal subjects. In the same study the airway hyperresponsiveness in patients with asthma was demonstrated, which is the defining physiological abnormality of this disease and remains an important target of asthma therapy [137]. The use of antihistamines for asthma is

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theoretical, since these drugs tested in asthma have demonstrated disappointing results. Even with the development of much more potent non-sedating H1-receptor antagonists, there is no clinical benefit in patients with asthma. However, in patients with allergic rhinitis and concomitant asthma it has been reported that unlike many other second-generation histamine H1-receptor antagonists, desloratadine provides the added benefit of efficacy against nasal obstruction in SAR [138].

On human isolated bronchus preparations, the cysteinyl leukotrienes [i.e. leukotriene C4 (LTC4) and leukotriene D4 (LTD4) and leukotriene E4 (LTE4)] are at least 1000 times more potent than histamine in causing smooth muscle contraction, with a long duration of action [139]. However, the concentration required to achieve a given bronchoconstrictor response varies considerably between individuals [140]. Although the airways of asthmatic patients in vivo are more responsive to LTC4, LTD4 and LTE4 than those of non-asthmatics [141]. Leukotrienes are produced by neutrophils, macrophages, basophils, eosinophils and monocytes. Two sub-groups of CysLT receptors have been recognized. Those blocked by known antagonists are termed CysLT1 receptors, and those that are resistant to blockade are known as CysLT2 receptors. In human airway smooth muscle, LTC4, LTD4 and LTE4 all activate CysLT1 receptors [142].

However, no correlation is found between clinical asthma severity, as measured by the degree of airflow obstruction or bronchial hyper-responsiveness, and the level of LTE, in the urine of stable asthmatic subjects [143]. The current leukotriene antagonists act at CysLT1 receptors, i.e. montelukast, no specific blockers of CysLT2 receptors have yet been identified [144].

Elderly patients with mild bronchial asthma classified as steps 1 and 2, treated with pranlukast monotherapy, a leukotriene receptor antagonist sold in Japan, presented a superior compliance to inhaled bronchial steroid therapy and it would produce an equivalent level of clinical efficacy to the monotherapy with inhaled bronchial steroid therapy [95].

9.2.5 Allergen specific Immunotherapy

In younger patients that have persistent symptoms despite medical treatment, allergen specific immunotherapy (ASIT) may be considered [145]. Allergen immunotherapy involves the subcutaneous and more recently, sublingual, administration of antigens to which the patient is sensitized. Most studies of immunotherapy for treatment of respiratory allergic disease have excluded older patients because of safety concerns, e.g. risks of developing anaphylaxis, particularly in patients taking a β-adrenoceptor antagonist who may not respond to rescue adrenaline. However, according to the latest update of the American Academy of Allergy, Asthma & Immunology (AAAAI), of the American College of Allergy, Asthma & Immunology (ACAAI); and of the Joint Council of Allergy, Asthma & Immunology, there is no absolute upper age limit for initiation of immunotherapy.

Using the following terms: elderly, immunotherapy, allergic rhinitis, asthma, we found one article in PubMed [146], and one abstract in Google [147]. ASIT can be considered an effective therapeutic option in otherwise healthy elderly patients with a short disease duration whose symptoms cannot be adequately controlled by drug therapies alone [146].
10. Conclusions

Although allergic diseases, as asthma, are commonly thought of as pediatric diseases, asthma is common in older patients but is frequently under diagnosed or diagnosed as chronic obstructive pulmonary disease. The first step in the treatment of asthma in older patients is to consider differential diagnosis. Although diagnostic techniques are generally the same in younger and older patients, in the latter age groups several other diseases must be considered in the differential diagnosis. Treatment of asthma in older patients is complicated by the presence potential for other co-morbid conditions and for the possible drug interactions. Furthermore, research on pathogenesis and guidelines for therapy of allergic diseases in older patients are limited, making treatment more difficult. These disorders can interfere with the patient's quality of life and in the case of asthma can cause significant morbidity and mortality. Therefore as the study of population ages it is critical to understand how to diagnose and treat asthma in older patients.

11. Financial and competing interests dislousure

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Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

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