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Review Article

Diagnosis and management of asthma in the elderly

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ABSTRACT

Bronchial asthma is one of the most common chronic diseases worldwide, and by definition not expected to recover with aging. However, the concept that asthma can affect older individuals has been largely denied in the past. In clinical practice, asthma that occurs in the most advanced ages is often diagnosed as COPD, thus leading to undertreatment or improper treatment. The heterogeneity of clinical and functional presentation of geriatric asthma, including the partial loss of reversibility and of the allergic component, contributes to this misconception. A large body of evidence has accumulated demonstrating that the prevalence of asthma in the most advanced ages is similar to that in younger ages. The frequent coexistence of comorbid conditions in older patients compared to younger asthmatics, together with age-associated changes of the human lung, may render the management of asthma a complicated task. The article addresses the main issues related to the diagnosis and treatment of asthma in the geriatric age.

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1. Introduction

A 78-year-old, never smoker female went to the emergency room for worsening dyspnea that had been preceded by fever with body temperature up to 38 °C. Chest physical examination revealed diffuse wheezing, rhythmic tachycardic heart sounds, and no peripheral edema. The chest X-ray was negative for parenchymal or pleural lesions; the arterial blood gas analysis showed partial respiratory failure with pH 7.41, PaO₂ 54 mm Hg, and PaCO₂ 39 mm Hg, on room air. Blood tests showed high levels of inflammatory markers and mild leukocytosis with a predominance of neutrophils. Among the anamnestic data, the patient reported several episodes of bronchitis and allergic reactions to some unspecified drugs. The son of the patient reported multiple sensitizations to aeroallergens. Of note, she suffered from depression and arterial hypertension, for which she was not assuming any treatment, and diffuse arthritis of the hands. The patient was admitted in the Department of Pulmonology with a diagnosis of acute exacerbation of chronic obstructive pulmonary disease (COPD).

She was treated with broad-spectrum antibiotics, systemic corticosteroids and inhaled bronchodilators with rapid resolution of respiratory failure and bronchospasm. However, the clinical course of the first days of hospitalization was characterized by several episodes of acute dyspnea associated with bronchoconstriction, which however were not properly described, thus postponing the extemporaneous therapy with bronchodilators and intravenous corticosteroids. In the following

days, she developed hyperglycemia, and had to be treated with subcutaneous insulin.

The clinical course improved after 10 days. Pulmonary function tests performed just before discharge (during bronchodilator therapy) showed moderate obstructive ventilatory defect. The patient was discharged with inhaled therapy including inhaled corticosteroids (CSI), long acting beta-2 adrenergics (LABA) and long acting muscarinic antagonists (LAMA). On subsequent outpatient visits, pulmonary function tests were repeated and showed improvement with mild obstructive defect after one month, forced expiratory volume in 1 s (FEV₁) % predicted was within normal limits after three months.

The case presented describes a typical presentation of bronchial asthma in later life. It is worth noticing that the respiratory symptoms in the elderly often lead to an erroneous diagnosis of COPD and management if usually complicated by the occurrence of comorbid conditions. Some information from the medical history (including allergic diathesis and the absence of cigarette smoking exposure), together with the reversibility of bronchial obstruction, allowed abandoning the hypothesis of COPD in favor of bronchial asthma.

In this review we describe the cardinal features of asthma in the elderly, and address the main aspects that should be taken into account when approaching an elderly individual complaining of symptoms suggestive of asthma.

1.1. Is asthma a rare disease in the elderly?

Our patient presented with symptoms that were interpreted by the physicians as clinical manifestations of COPD, although she had never smoked and had not referred a previous diagnosis of chronic bronchitis. This is because a common belief attributes to asthma the definition of

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“rare” disease when occurring in the geriatric age. One of the issues is related to the definition of “elderly”: the majority of the epidemiological as well as clinical studies that are described in this review agree on the cut-off value of 65 years of age. Indeed, this age group is the fastest growing proportion of the first world population, expecting to represent up to 17% of the total world population in 2050 [1]. The precise prevalence of asthma in the elderly is difficult to ascertain. This is due to the current absence of universal criteria for the diagnosis in this age group, which are mainly related to the heterogeneity of the clinical and functional presentations of the disease in this population, including the partial loss of reversibility, and the poor perception of symptoms by the patients [2]. A large body of evidence has accumulated in recent years confirming that the prevalence of asthma in the most advanced ages is similar to that in younger ages. Several studies in the European and U.S. populations showed that asthma is common among the elderly: its prevalence among people aged over 65 years ranges from 1.8% to 10.9%, with the highest rates in males and with a slight increase over time [3–14]. The estimated incidence of asthma in the elderly is about 95 per 100,000 subjects, with a reduction from 103 per 100,000 in subjects aged 65–74 years to 58 per 100,000 in those aged >85 years [15]. Older asthmatics have the highest mortality rate (51.3 per million people) of any other age group [16]. Bellia et al. [17] demonstrated that asthma in the elderly was associated with a higher mortality rate compared to that in control subjects (24.3% vs. 16.3%, respectively).

1.2. What are the features of elderly asthmatic patients?

Our patient presented with acute dyspnea, which is a common denominator of several respiratory diseases. Indeed, asthma in the elderly often overlaps with a variety of structural and functional changes associated with the physiological aging of the respiratory system, as well as with many diseases that are common in advanced age. Elderly subjects suffering from asthma can be divided at least into two groups (Table 1): patients with a longstanding asthma, and those in whom the symptoms occur later in life (after the age of 65 years) [18]. Studies have demonstrated that patients with a longstanding disease, contrary to those with late-onset asthma, have worse and more frequent respiratory symptoms, increased number of hospitalizations and emergency medical interventions, and lower values of spirometric parameters [19,20]. Indeed, patients with long-standing asthma tend to have more severe and irreversible, or partially reversible, airway obstruction than those with late onset asthma [21,22]. Asthmatic subjects were demonstrated to be differently affected by obesity based on whether their asthma occurred early (<12 years of age) or later in life [23], a significant association between increasing BMI and duration of asthma only occurring in early-onset asthma, potentially affecting the response to treatment.

On the other hand, a higher annual decrease in FEV₁ is observed in patients with newly diagnosed disease [24], and in patients with early-onset non-atopic asthma, which represents the main phenotype in elderly subjects [25]. Atopy seems more frequent in patients with early-onset asthma than in those with late-onset disease. The question is whether atopy per se affects the asthmatic phenotype in this population. In the Normative Aging Study [26], the role of the allergic response to environmental aeroallergens in the development of asthma in older men was assessed. Subjects in whom airway hyperresponsiveness on

methacholine challenge occurred had a higher prevalence of serum IgE reactivity to cat allergen and *Dermatophagoides* when compared to normoreactive individuals. Older individuals spend more time in the same indoor environment compared with younger adults, and it is conceivable that the impact of environmental control, particularly for indoor allergens (mites, molds, pets and cockroaches), will be higher in this age group. Although available data seem to favor the decline of allergen sensitization with age, the prevalence of allergic sensitizations in the elderly population with respiratory symptoms is substantial enough to warrant evaluation of the atopic condition [27]. The identification of an allergic component of asthma in the elderly patient may influence treatment. Indeed, the recognition of allergens as possibly responsible for the respiratory condition allows preventive environmental strategies to be applied, and allergen specific immunotherapy with effective adjuvants to increase the immune response while reducing the risk of systemic reaction to be conducted.

Breathlessness is the most common presenting symptom; it has been reported that 48% of asthmatics in older ages recall the onset of respiratory symptoms before 40 years of age [28]. Nevertheless, symptoms are often not properly attributed to asthma for a period of time, as in the case reported, in which the exacerbations of asthma were interpreted as episodes of acute bronchitis. In the context of the S.A.R.A. Study [29] only 50% of the elderly patients with carefully ascertained asthma had received a correct diagnosis; conversely, 20% of the study sample reported an erroneous diagnosis of COPD and/or emphysema and, even more worrying, more than 27% of the asthmatics had never received any diagnosis of respiratory diseases. In addition to dyspnea, cough can represent a relevant symptom but rarely is the only presenting one. Cough efficacy may be markedly reduced in the elderly because of age-related or comorbidity-related impairment of both motor and sensory components [30].

Accumulating evidence shows that in a not trivial proportion of elderly subjects, a coexistence of asthma and chronic bronchitis may occur [31], suggesting the occurrence of an overlap phenotype. In addition, the concomitant occurrence of bronchiectasis is associated with more severe asthma, more frequent hospitalizations due to asthma exacerbation and more frequent occurrence of chronic respiratory failure. Finally, air pollution has been shown to significantly correlate with increased emergency room admissions for asthma in elderly asthmatic patients, mostly in subjects aged more than 65 years, even in warm seasons [32].

1.3. How to diagnose asthma in advanced ages

Our patient was erroneously diagnosed as affected by COPD. This usually occurs because of a cultural bias that associates asthma to childhood and adolescence. Asthma in the elderly is frequently underdiagnosed and as a result, undertreated [29,33]. The main task in establishing the diagnosis in advanced ages is to distinguish asthma from COPD. Indeed, both diseases are characterized by chronic bronchial inflammation and by an obstructive functional pattern [34]. Some of the diagnostic mistakes are due to the erroneous concept that airway obstruction in young ages invariably suggests the occurrence of asthma, while the same spirometric findings in older adults are usually attributed to COPD, even in the presence of reversibility of the obstruction and in subjects without smoke exposure [35]. Conversely, it has been observed that patients over 64 years old, hospitalized with a diagnosis of asthma, frequently received a diagnosis of COPD in the following hospitalizations [36]. Age per se appears to be the main confounding factor in the differential diagnosis between asthma and COPD; this is further highlighted by the fact that elderly patients often do not perceive (and properly describe) chest tightness associated with bronchospasm, as it occurred in our patient, and tend to adopt a sedentary lifestyle that contributes to the subjective underestimation of respiratory symptoms [29,33,36–38].

Table 1

Main clinical and functional differences between early and late onset asthma.

	Early-onset asthma	Late-onset asthma
Atopy	+++	+
Symptoms	+++	+
Pulmonary function impairment	+++	+
Annual decline in FEV ₁	+	+++
Obstruction reversibility	++	+++
AHR	++	++

AHR: airway hyperresponsiveness; FEV₁: forced expiratory volume in 1 s.

Factors suggesting the diagnosis of asthma include onset in childhood, atopy, and nocturnal or morning respiratory symptoms. However, none of them is sufficient to pose a definite diagnosis. Several studies showed that the prevalence of allergen sensitizations decreases with aging [39,40], as the result of age-related modifications of the immune system, defined as immunosenescence. Furthermore, a reduced awareness of the night-time bronchoconstriction has been described [41].

Pulmonary function tests with the measurement of lung volumes and the evaluation of reversibility of bronchial obstruction remain the hallmark for the diagnosis of asthma at all ages. Nonetheless, many aspects of the interpretation of the findings (choice of suitable cut-off diagnostic levels, appropriate reference values and sound criteria for evaluation of reversibility) are still controversial [42]. Unlike what is commonly believed, there is strong evidence that acceptable spirometries and reversibility tests can be obtained in the majority of elderly respiratory patients [43–45]. When spirometry shows bronchial obstruction, it is mandatory to perform a bronchodilator reversibility test. It should be taken into account that reversibility of airway obstruction in elderly asthmatics is often reduced because of irreversible structural changes, due to remodeling of the airways [46]. On the other hand, in COPD patients a significant response to bronchodilator can be observed. In this regard, the achievement of normal lung function and the assessment of bronchial reversibility at different time frames are crucial. In addition, the degree of bronchial reversibility can be evaluated as a response to regular treatment over a period of time. In the case reported the reversibility of airway obstruction was highlighted only after several weeks of therapy and was large enough to bring the FEV₁ within the normal range, thus excluding the diagnosis of COPD. Finally, the measurement of the carbon monoxide diffusing capacity of the lungs (DLCO) and of residual volume (RV) can help in the differential diagnosis. Indeed, COPD subjects with a comparable degree of bronchial obstruction than asthmatics have more frequently a reduction of the former and an increase of the latter functional parameter [47]. These lung function tests should be implemented in clinical settings; in the case described, the results of such tests, if performed, would have facilitated the correct diagnosis.

Airway hyperresponsiveness (AHR) plays a crucial role in the pathogenesis of asthma at any age. Thus, tests aimed at the detection of AHR may be useful for differential diagnosis of asthma in the elderly. With this in mind, it should be considered that aging is associated with structural and physiological modifications of the lung [48], which influence the airway response to spasmogenic stimuli and, consequently, the characteristics of the asthmatic phenotype in this population. It is yet to be demonstrated whether the slope of the dose–response curve during the bronchoprovocation test, rather than the magnitude of bronchial responsiveness, can help in differentiating the airway response to spasmogen between asthma and COPD in the elderly.

In addition to pulmonary function tests, the assessment of the inflammatory markers by induced sputum and the degree of airway remodeling by imaging techniques might be useful to characterize phenotypically patients with coexisting asthma and COPD. With regard to the smoking history, not surprisingly a high proportion of elderly asthmatics have been smoking in spite of the disease. In a study conducted on elderly asthmatics [15], the history of tobacco smoking occurred in more than half of the study population. Thus, the current or former exposure to smoke is not a discriminating factor when diagnosing asthma in the older ages. On the other hand, given that cigarette smoke remains the main risk factor for the development of COPD, the lack of tobacco exposure in individuals with chronic obstructive symptoms favors the diagnosis of asthma. The diagnostic process in our patient would have certainly benefited from the reported absence of smoke exposure in her life.

In conclusion, the distinction between asthma and COPD in an older individual can be confounded by the progression of common pathogenetic mechanisms induced by different environmental agents, or different disease mechanisms leading to an overlapping clinical

syndrome. The overlap syndrome has significant impact on health resources in that such patients are affected by worse control of their symptoms and more frequent comorbid conditions. In addition, little is known on how best to treat those subjects since they are systematically excluded from clinical trials and are not covered by treatment guidelines.

1.4. What is the role of comorbidity?

Our patient reported the coexistence of at least three comorbidities: depression, arterial hypertension, and arthritis. In addition, hyperglycemia developed during her admission at the hospital. The presence of multiple illnesses is the norm in the elderly patient as a result of two processes: the association between age and incidence of degenerative diseases, and the development over time of complications of the existing diseases. Indeed, comorbidity is considered one of the hallmarks of the geriatric patient, and a fundamental component of their complexity.

Asthma per se is associated with an increased risk of comorbidity regardless of age. An analysis of administrative data on health care expenditures showed that adults with asthma have on average 3.1 chronic comorbidities compared to 1.9 in people without asthma [49]. A cross-sectional study analyzing data voluntarily collected by general practitioners in Italy [50] showed an association, albeit weak, between asthma and depression, diabetes mellitus, osteoporosis, and gastroesophageal reflux disease. In a cohort of patients aged 65 years or older, Soriano et al. reported an association between asthma and diseases of different organ systems (especially cardiac and respiratory), with an increased risk of incident pneumonia, respiratory infections, myocardial infarction, and angina [51]. It is interesting that this pattern of comorbidities is different from that observed in younger asthmatics, but resembles the one observed in chronic obstructive pulmonary disease. As previously discussed, COPD itself is an important comorbidity of asthma, and the prevalence of overlap between these two diseases increases with age [52]. Furthermore, older people with long-standing asthma may develop “fixed” bronchial obstruction [53].

Compared to people without asthma, people with asthma have an increased risk of disturbed sleep [54], and this comorbidity should not be overlooked in the elderly, as it may contribute to the high prevalence of depression in this population [55]. The complexity of the elderly, comorbid patient may account for the poorer outcome of asthma in this group compared to younger people. Most of the deaths due to asthma occur in elderly people [56], and elderly asthmatics also have a higher all-cause mortality, although asthma itself does not seem to increase the mortality risk [17]. Comorbidities also are an important driver of asthma-related costs [57]. The presence of comorbidities influences quality of life: among adults with asthma, about one third of those reporting comorbidities also reported to have a poor quality of life [58].

An important aspect when addressing the role of comorbidity is its interaction with drug therapy. It is not surprising that our patient developed hyperglycemia, probably because of the high doses of systemic corticosteroids. This often occurs in elderly subjects with impaired glucose tolerance as a result of the acute stressful event and the use of systemic corticosteroids. In addition, depression most likely contributed to confuse the diagnosis. If properly assessed, the correct management of comorbidities would have accelerated the diagnosis. Comorbidity is associated with polypharmacotherapy, which in turn is one of the most important risk factors for adverse drug reactions in the elderly [59]. The risk for adverse drug reactions is further increased in this population by the high prevalence of renal insufficiency that often goes unrecognized due to lack of serum creatinine increase [60]. Furthermore, specific comorbidities may impair the ability to use inhalation devices, and this is the case of our patient who was suffering from arthritis. For example, a strong relationship between cognitive function evaluated using standard screening tests (e.g., the Mini-Mental State

Examination) and the ability to acquire metered dose inhaler or Turbohaler technique has been shown [61].

1.5. How to manage asthma in advanced ages

1.5.1. Multidimensional assessment

As all other diseases, asthma cannot be adequately managed in the elderly without taking into account the complexity that is inherent to these patients. This paradigm has led to the concept of “multidimensional assessment” (MDA), defined as “a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible” [62]. MDA is a fundamental tool in geriatric medicine as it allows identifying priorities and strategies in the management of these patients. A comprehensive description of MDA techniques is beyond the scope of this article; therefore we will only focus on those aspects that become crucial when evaluating the geriatric asthmatic patient.

Evaluation of cognitive function is of importance both for asthma severity assessment, which requires the ability to report asthma-related symptoms, and for compliance to drug therapy (see below). Different screening tools are available, such as the Mini-Mental State Examination (MMSE) that is commonly used in the elderly population. The MMSE lacks information on the psychometric characteristics of the elderly asthmatic population. The poor performance of the MMSE is probably due to the peculiar pattern of cognitive deficits in elderly people with respiratory problems, in which verbal memory and executive function seem to be more impaired [63]. On this basis, the MDA of elderly patients with asthma should also include a test for verbal memory (e.g., the Rey 15-item memory test) and for executive/praxic function (e.g., the Clock test).

Mood status should be routinely investigated as it is strongly related to compliance to therapy, poor quality of life, and poor outcomes in elderly with asthma [64]. Furthermore, anxiety and depression are related with overperception or underperception of asthma symptoms, and thus may lead to a misclassification of asthma severity [65]. A further investigation by Di Marco et al. showed a close correlation between anxiety and depression, and a poor asthma control [66]. Our patient did not adequately perceive, and therefore, reported chest tightness associated with episodes of bronchospasm. This may have delayed the correct diagnosis and assessment of disease severity. Different questionnaires are available to evaluate depression in the elderly, including the

Geriatric Depression Scale and the Hospital Anxiety and Depression Scale.

Physical function can be considered an overall marker of health in the elderly. In particular, gait speed is related to quality of life, incident disability and mortality [67]. Consequently, evaluation of walking speed is included in almost all MDA protocols. Different methods for gait speed evaluation exist, with variable distances (4 or 6 m, 15 ft, etc.) and effort (usual pace vs. as fast), with no significant differences with respect to their ability to predict survival [68]. In patients with respiratory diseases, the 6-min walking test (6MWT) is commonly used as a sub-maximal exercise test. While longer to administer, the 6MWT seems preferable because it allows the detection of functional limitations due to poor lung function. Again, we predict that our patient would have benefited from a multidimensional assessment, both in terms of early diagnosis and proper treatment. Fig. 1 describes the main steps that should be performed when approaching an individual with suspected asthma in the elderly.

1.5.2. Pharmacological treatment

As a general concept that applies to all ages, the effort to avoid triggers that can precipitate asthma should be encouraged. All elderly patients with asthma should also receive annual influenza vaccine prophylaxis and pneumococcal vaccine administration when indicated [69], to reduce the risk of viral or bacterial infections that can cause severe asthma attacks. Active interventions, such as smoking cessation and reduction of body weight, should always be pursued, whenever necessary. Also, with the advantages of more effective or easier methods of specific allergy treatment (e.g., subcutaneous immunotherapy with adjuvants to increase the immune response, sublingual immunotherapy) elderly patients may be managed more effectively [70,71].

The management of asthma in the elderly follows specific guidelines that apply to all ages [72], although most behaviors are an arbitrary extrapolation of what has been tested in young ages. In fact, age has always represented an exclusion criterion for eligibility to clinical trials. Inhaled corticosteroids remain the mainstay for the treatment of persistent asthma, even in older populations. Local adverse effects (hoarseness, cough, candidiasis) can be more frequent in older patients, because of oral deposition due to lack of coordination when using the device, and could be avoided by using a spacer or a chamber, and by inviting the patients to rinse his/her mouth after each inhalation. Among potential side effects, the attention must be focused on cataracts and

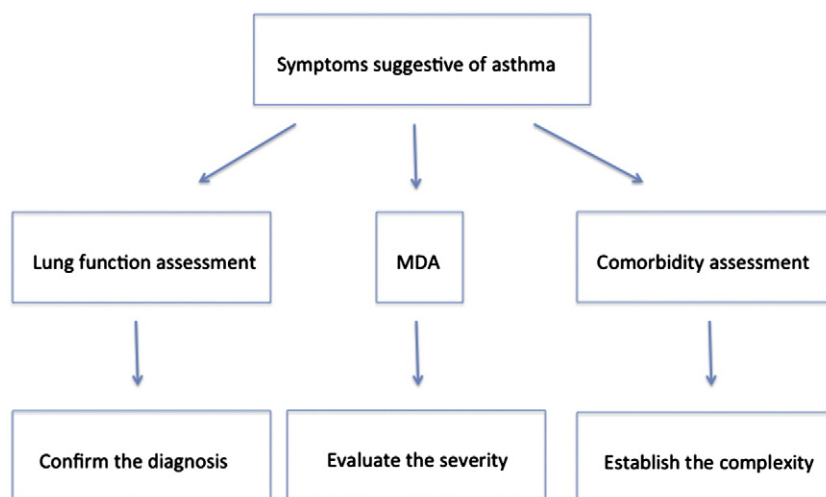


Fig. 1. A suggested approach to an individual with suspected asthma in older age. MDA: Multidimensional assessment. Lung function assessment should include spirometry with reversibility test and measurement of the carbon monoxide diffusing capacity of the lungs (DLCO). MDA should include the Geriatric Depression Scale (GDS), the Mini Mental State Examination (MMSE), and the six minute walking test (6MWT).

osteoporosis since they represent frequent comorbidities in the elderly population. A higher risk of systemic side effects is associated with the chronic administration of oral corticosteroids: for this reason, dosages and duration of treatment should be carefully controlled.

Long acting beta-2 adrenergics exert both a valid and prolonged bronchodilation and a steroid sparing effect when added to moderate dose inhaled corticosteroids instead of increasing the dosage of the latter. At usual therapeutic doses side effects are rare and include muscular tremors and tachycardia. However, the coexistence of cardiovascular disorders increases the frequency and severity of side effects, some of which may be particularly detrimental in elderly patients [73]. Of note, aging-related impairment in responsiveness to bronchodilators has been observed in vivo and in vitro [74,75]. Anticholinergic drugs may represent a valid alternative to beta-2 agonists. Although they have not yet been approved for asthma by the normative authorities, there is a rationale to support their use in elderly asthmatics. Theoretically, anticholinergics may induce urinary hesitancy, constipation and exacerbations of glaucoma, all of which would be significant in elderly patients. However, only few studies have been conducted to assess this issue in asthma. In a recent small study on asthmatic age 41–82 years with and without emphysema, the only adverse effect of inhaled tiotropium was dry mouth [76].

Antileukotrienes may have advantages over inhaled bronchodilators as additive treatment with corticosteroids, when the former are contraindicated in older populations due to concomitant diseases. Theophylline is a bronchodilator agent that has been used for various decades in the treatment of asthma. This drug may cause cardiovascular side effects such as supraventricular tachycardia and arrhythmias including also potential fatal events like ventricular arrhythmias. The difficulties in managing this drug in terms of dosage adjustment and side effects limit its use in the elderly. A possible therapeutic option for elderly patients with severe allergic asthma is anti-IgE therapy with the monoclonal antibody omalizumab. This has recently been shown to be effective in decreasing symptoms in elderly population, especially in those subjects with early onset of disease. Possible unwanted effects of anti-IgE therapy include an increased risk of parasitic infection and adrenal insufficiency, which should be properly addressed in the advanced ages [77,78].

1.6. Are pharmacokinetics and pharmacodynamics of asthma drugs different in the elderly?

The mainstay of asthma management is to achieve and maintain control of the disease, by periodically reassessing clinical and functional parameters. In the elderly, special attention should be paid to the safety of treatment as well, since this can be influenced by age-related factors, such as the more frequent occurrence of comorbidities and prescription of multiple drugs. Older people experience more adverse drug effects because of pharmacodynamic and pharmacokinetic changes and particularly drug–drug and drug–disease interactions. Bronchoconstriction affects drug deposition, with distribution being less uniform in individuals with obstructive airways. This has been demonstrated with inhaled corticosteroids administered using powder inhalers: beclomethasone, budesonide, fluticasone propionate and mometasone furoate [79]. For these four drugs the systemic absorption at 50% predicted FEV₁ was about 23%, 23%, 29% and 54% less compared with 100% predicted FEV₁ [79]. Since these correlations were stronger after adjusting for age, the authors suggest that factors other than lung function affect the systemic absorption of inhaled corticosteroids. We speculate that in the elderly patients age-related factors, such as reduction in lung function, interfere with systemic absorption of inhaled corticosteroids and perhaps with absorption of all inhaled drugs.

Looking at the use of bronchodilators in the treatment of airway obstruction in elderly patients [80], there is evidence for modification of pharmacokinetics and/or pharmacodynamics of beta-agonists, anticholinergics and theophylline [81]. The beta-adrenoceptor response is

different due to increased sympathetic system activity, reduction in adenylyl cyclase responses and reduction in beta-adrenoceptor affinity with aging [81]. Similarly, the anticholinergic response is different due to the decrease of parasympathetic activity and reduction in receptor numbers or post-receptor coupling, as, demonstrated in animal models, with aging [81].

Whether the aging process is associated with changes in theophylline kinetics has been a matter of controversy. A large number of studies demonstrated that theophylline metabolism decreases in the elderly [82–85] although data are conflicting [86,87]. Adverse events of theophylline may develop also in patients who are taking the usual dose because the clearance of theophylline is modified by various factors, including aging. In this respect, it has been reported that theophylline clearance gradually decreases with age. However, some authors demonstrated that changes in theophylline clearance only become apparent in the last decades of life [88] and that adult age is a relatively weak predictor of theophylline clearance [83]. Moreover, Ohta et al. [89] investigated 3810 Japanese elderly patients and demonstrated that those with liver disorders and those with concomitant arrhythmia more frequently showed adverse events of theophylline with an odds ratio of 1.81 and 1.88, respectively.

1.7. Does adherence to treatment play a role in the elderly?

As in all chronic diseases, careful attention should be paid to the adherence to therapy particularly in older subjects, who often suffer from comorbidities and are put on complex treatment regimens including several different drugs: both factors can negatively influence the compliance of the asthmatic patient, thus limiting the efficacy of any therapeutic scheme. Physical and cognitive impairment, together with depression, may affect the adherence of elderly patients to treatment plan [90,91]. Finally, adverse reactions related to polypharmacy and to comorbidity are more frequent in the elderly: on the one hand bronchodilators might worsen coexisting diseases (such as cardiac arrhythmias); on the other hand, medications often used by elderly patients, like β -adrenergic blockers or non-steroidal anti-inflammatory drugs, might elicit or worsen bronchoconstriction. Asthma treatment is often based on medications, dispensed through specific devices: problems connected with the use of complex inhalers are common in this age range, which in turn affect adherence to treatment. There is no doubt that the ideal inhaler should be simple to use and to carry, and should assure the optimal and consistent delivery of the drug. A recent Italian survey demonstrated that a good patient–physician relationship represents the first step for a successful management of respiratory diseases [92]. A retrospective study on the prescription refill adherence for inhaled therapy dispensed to asthma /COPD patients aged 60 years and older over a 10-year period demonstrated that only 28% of the repeat prescriptions for inhaled corticosteroids had been dispensed with a satisfactory refill adherence [93]. Recently, asthma outcomes in older people were demonstrated to be significantly improved by delivering tailored education that identifies specific patient concerns and unmet needs [94]. In our patient, there is no mention of educational plans adopted by the physicians, explanation and reassessment of the inhalation techniques, and choice of the device. All of them may have contributed to a slower recovery.

2. Conclusions

Today, asthma in the elderly is a well-recognized condition, with unique features reflecting the co-existence of other diseases, the use of multiple respiratory and non-respiratory drugs, individual responsiveness to treatment, and different perceptions of symptoms. The prevalence of asthma in older adults has been demonstrated to be not different from that in younger adults, ranging from 6 to 10%. Given the progressive aging of population, it is plausible to predict that asthma in the elderly will markedly increase its impact on public health in the

next years. Efforts should be made to disseminate the knowledge on this nosological entity, in order to help the physicians to properly recognize and treat the older asthmatics.

Learning points

- The precise prevalence of asthma in the elderly is difficult to ascertain, because of the heterogeneity of the clinical and functional presentations of the disease at advanced ages, including the partial loss of reversibility and the poor perception of symptoms by the patients. It is however assumed that the prevalence of asthma in the most advanced ages is similar to that in younger ages.
- In clinical practice, asthma that occurs in the most advanced ages is often diagnosed as COPD, thus leading to undertreatment of improper treatment. This is mainly due to the erroneous concept that airway obstruction in older adults is usually attributed to COPD, even in the presence of reversibility of the obstruction and in subjects without smoke exposure.
- Pulmonary function tests with the measurement of lung volumes and the evaluation of reversibility of bronchial obstruction remain the hallmark for the diagnosis of asthma at all ages. In this context, the choice of suitable cut-off diagnostic levels, appropriate reference values and sound criteria for evaluation of reversibility is crucial.
- The presence of multiple comorbid conditions is the norm in the elderly patient and comorbidities should always be assessed. Cognitive function and mood status should be routinely investigated as they are strongly related to adherence to therapy, quality of life, and poor outcomes in elderly asthmatics.
- The management of asthma in the elderly follows specific guidelines that apply to all ages, although most behaviors are an arbitrary extrapolation of what has been tested in young populations.

Conflict of interests

The authors declare no conflict of interest related to this review article.

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