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BRN Rev. 2023;9(2):110-124

BRN Reviews

REVIEW ARTICLE

Asthma in the Elderly: Systematic Approach to Improve the Prognosis

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ABSTRACT

The objective of this review is to summarize the key points of asthma in elderly people including epidemiology, pathophysiology, clinical presentation and diagnosis and treatment. Although asthma was long considered a childhood disease, now it is clear that the disease is frequently diagnosed in adults over 65 years, with an incidence similar to that shown in other age groups. Furthermore, in advanced age population asthma is more severe, with more frequent exacerbations and higher mortality rate. From a pathophysiological point of view, two key processes are produced, immunosenescence and anatomical and mechanical changes with direct impact on lung function. The diagnosis should follow the same principles as the general population. However, underdiagnosis is frequent due to several factor such as comorbidities, poor perception of symptoms and reduction in physical activity. The treatment of these patients should pay particular attention to polypharmacy and multimorbidity.

Keywords: Asthma. Elderly patients. Immunosenescence. Multimorbidity. Polypharmacy.

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Received in original form: 06-06-2023
Accepted in final form: 22-06-2023
DOI: 10.23866/BRNRev:2023-M0086
www.brnreviews.com

INTRODUCTION

The American Thoracic Society (ATS) considers individuals older than 65 years as elderly, but the United Nations (UN) include those over 60 years old in this respect[1-3]. Age is a determining factor in defining the elderly, but it is not the only one, since the sociodemographic and physiological characteristics that determine physical and cognitive function must also be taken into account[2].

The advanced age population (AAP) constitutes an increasingly greater percentage of the population in Western countries. On 1 January 2017, in Spain, there were 8,764,204 people of 65 years or older, which is 18.8% of the total population. The estimate for the year 2066 is that it will reach 14 million people, or 35% of the total[4].

Aging, which is defined as an array of time-dependent functional impaired changes of physiological, epigenomic, metabolic, and immunological alterations, is the key player in regulating longevity[5].

Asthma was long considered a childhood disease, with little attention being paid to its possible diagnosis in elderly people. In the 1980s, this view began to change, due to the results of the Tucson study, where it was shown that asthma was frequent in adults over 65 years, often severe, and was associated with relatively high mortality rates[6].

EPIDEMIOLOGY

Different studies have shown us that the prevalence of asthma in the AAP varies between 2.5% and 13%, similar to that in young adults[7-11]. These data are probably an underestimate, as asthma in the elderly is under-diagnosed and under-treated[1,10,12,13].

The incidence of asthma in this age group is also significant. In a study carried out on a general population in Norway, with a follow-up of 11 years, an accumulated asthma incidence of 5.8% was obtained in the 50-70-year age group, higher than the 3.4% in the individuals of 30-49 years and doubling the 2.6% in the 15-29 year-olds[14]. In a similar study carried out on a population of Cracow, Poland, and Tucson, Arizona, USA, with a 13-year follow-up, the odds ratio of incidence of asthma medically diagnosed in the 56-70-year population was 2.3 in Cracow and 1.4 in Tucson, with the 19-40 years group being the reference[15].

It has also been seen that the severity of asthma increases with age. The percentage of asthmatics with severe disease varies between 12.5% and 13.4%, whilst that for those under 40 years, it falls to values between 6.6% and 8.8%[16]. Furthermore, at least in some countries, the percentage of patients over 60 years with severe asthma appears to be increasing. In Korea, in the year 2022, the percentage of patients with severe asthma was 54.7%, while it was 63.1% in 2015[17]. On the other hand, the AAP shows higher rates of exacerbations, hospital admissions, mortality, life threatening episodes, and higher disease costs[18.19].

In a study carried out on a Danish population, comparing asthmatics over 70 years old with a group of 15- to 45-year-olds, it was observed that the incidence of exacerbations was 6.3 times higher, and the mortality associated with asthma was nine times greater[19]. Another study performed in Galicia found that more than 80% of those that died due to asthma were over

65 years old[20]. This aligned with the results obtained by Tsai et al.[21], where asthmatics over 65 years old had a mortality, adjusted for co-morbidities, of four times that of those younger than that age. It has also been seen that two-thirds of the hospital admissions resulting in death due to asthma were in individuals over 60 years old, particularly in women, and that they also had a longer hospital stay[22]. The cost generated by the disease is increased by 50% in individuals over 65 years old compared with those below this age[23].

Among elderly asthmatics, the risk of exacerbation or hospital admission is increased in those with clinical morbidities, mold in the home, financial barriers to asthma-related health care, fixed airway obstruction, a prior history of exacerbations, psychiatric illness, cardiovascular disease, non-eosinophilic inflammation, cachexia, food allergy, household exposure to disinfectants and cleaning products, poor asthma control, and male sex (Table 1)[24-28].

Table 1. Main epidemiological characteristics of asthma in the elderly in comparison with younger people

High prevalence, similar to young adults
Higher mortality rate
More severe
More frequent exacerbations

PATHOPHYSIOLOGY

Aging is the result of the accumulation of molecular and cellular damage throughout life. Regarding asthma, with the passing of the years, two key processes are produced: immunosenescence and anatomical and mechanical changes with a direct impact on lung function.

IMMUNOSENESCENCE

Immunosenescence is defined as collective abnormal changes of the immune cells with age, which finally affects the disease process directly or indirectly[29]. These changes in the immune response, both innate and acquired, have clinical consequences, since they increase the susceptibility to infections, the malignancy rate, and autoimmune diseases[30-32].

Cellular senescence was initially discovered by Hayflick[33], who described a state of cell proliferation arrest in cultured human cells after several divisions. Up until now, several stimuli causing cellular senescence have been reported, including telomere shortening due to replication exhaustion, DNA damage, mitochondrial dysfunction, oxidative stress, certain cytokines, and loss of tumor suppressors[31-34].

The number of neutrophils in the peripheral circulation does not change with age, although there appear to be modifications in chemotaxis and phagocytic capacity, which could lead to a lower neutrophilic activity in the acute inflammatory response, and favor more frequent and more severe respiratory infections. In bronchoalveolar lavage studies in the airway, an increase is observed in neutrophils and associated inflammatory mediators, such as metalloproteinases, elastase, and interleukin-8. It has also been observed that there is a reduction in apoptotic mechanisms that favor neutrophil persistence[35,38].

The number of Natural Killer (NK) cells are increased with age, but their cytotoxic activity decreases. Natural Killer T (NKT) cells are reduced, leading to an imbalance between the NK and NKT cells, which could favor the exacerbations in relation to viral infections[11,35,36,38].

The macrophages in the airway are reduced. Toll-Like Receptors (TLR) contribute to germ recognition and elimination, and constitute a bridge between innate and adaptive immunity, promoting the presentation of antigens and a specific pattern of cytokinase secretion. The expression of TLR is reduced in the AAP and thus the monocytes stimulated by TLR produce less interleukin-6 and tumor necrosis factor alpha (TNF-α)[35,36].

In mouse models, it has been observed that the expression of Fc-gamma-RIIB/III in mastocytes is reduced with age. This a receptor involved in the antigen response process which modifies the antigen-presenting capacity[35-36].

The eosinophil count in the airway is similar to that in young people, although they seem to reduce functional capacity, they have a lower degranulation capacity in response to interleukin-5 in AAP than in young people[11,35].

Dendritic cells lose functional capacity, which leads to a lower phagocytosis capacity and a poorer immune response in vaccination[35,36,38].

Thymic involution occurs, leading to a reduction in the diversity of the T-cells receptor, with the resulting lower antigen-recognition capacity. This seems to be associated with a lower viral clearance in influenza A infections, and a lower response to antigens. The function of TH-17 and T-Reg cells also appear to be modified, but it is not well clarified[35,39].

The potential to generate Naive B cells is reduced as well as the activation of B-cells mediated by T-cells. The capacity to produce antibodies is maintained, but they have a lower affinity for antigens[35,39,40].

Chronic systemic inflammation increases, with an increase in the levels of interleukin-1, interleukin-6, and TNF-alpha (Table 2)[1,35-37,39].

IgE production and the prevalence of allergic sensitization is reduced[11,41].

Telomere shortening is one of the most common mediators in cell aging. Telomeres gradually shorten with each cell division, and when they reach a critical length, cell division capacity is affected[42].

A shortening of telomeres has been seen in asthmatics, such as fibroblasts, white cells or mononuclear cells. Furthermore, telomere shortening is associated with increased asthma severity and bronchial hyper-reactivity[42].

Although there is still doubt on whether telomere shortening accelerates the development of asthma or is a result of asthma, at present, the first option seems more probable; telomere shortening being the cause of greater inflammation in asthma. This could explain, at least in part, the incidence of asthma in the AAP[42].

Other factors associated with increasing immunosenescence in the incidence of asthma may be the oxidative stress that produces

Table 2. Immunosenescence: main changes

Neutrophils in peripheral blood	The number does not change
	Lower chemotaxis and phagocytic capacity
Neutrophils in airways	Increase in number
	Increase in neutrophilic inflammatory mediators
Natural Killer cells (NK)	Increase in number
	Decrease in cytotoxic activity
Natural Killer T cells (NKT)	Decrease in number
Macrophage	Decrease in number
Toll-Like receptors	Decrease expression
Eosinophils	The number does not change
	Diminished functional activity
Dendritic cells	Diminished functional activity
	Decrease phagocytic capacity
Humoral immunity	Reduced vaccine response

damage in the DNA, the chronic inflammation that may accelerate cellular senescence, alterations in cellular autophagy, due to being insufficient and non-selective, alterations in the respiratory epithelial cells, and the deterioration of mesenchymal cells[32,42].

ANATOMICAL AND MECHANICAL CHANGES

The collagen fibers that surround the alveolar ducts change, producing dilation of the alveoli, although it is different from that observed in emphysema, as it does not lead to destruction of the alveolar walls. This dilation reduces the superficial alveolar pressure and thus also reduces the elastic recoil pressure and compliance of the thoracic wall[1,11].

The degenerative changes of the vertebral column increase kyphosis, which, combined with the increase in sternal convexity increases the antero-posterior diameter of the chest. This leads to a decrease in thoracic compliance. It is estimated that approximately 30% of thoracic wall compliance is lost by the age of 75[1,11].

Respiratory muscles lose strength due to change in the diaphragmatic curvature, sarcopenia, and inadequate nutrition. Diaphragmatic strength is 25% lower at 76 years than that at 30 years[1,11,43].

These structural changes contribute to functional deterioration. In healthy non-smoker individuals, the forced expiratory volume in one second (FEV_1) decreases approximately 30 milliliters per year from the age of 30 years. The FEV_1/forced vital capacity (FVC) ratio is also reduced, favoring airflow obstruction. Furthermore, it leads to early closure of the airway due to the reduction in the elastic recoil of the lung and the reduction of the thoracic wall compliance. This leads to an increase in the residual volume (RV) and the residual functional capacity, with the resulting air entrapment and hyperinflation. The peak (maximum) inspiratory and expiratory pressures decrease significantly. The peak inspiratory pressure in males is reduced by about 35% between 50 and 80 years of age. The RV increases by 50% between 20 years and 70 years. Furthermore, it produces an increase in the bronchial reactivity in response to methacholine. These changes lead to alterations in the ventilation-perfusion ratio and an increase in the alveolar-arterial oxygen gradient[1,11]. On the other hand, it is known that impaired lung function in

midlife is associated with a greater risk of incident dementia and mild cognitive impairment later in life, which is a common comorbidity in AAP[44].

IMPACT OF GENDER

Given that asthma in the adult age predominates in women, the differences in the evolution of the disease in the female gender will be particularly relevant[45]. One of the pathophysiological processes to consider in women of advanced age is the menopause, since it is associated with significant physiological changes.

In a multicenter study carried out in the north of Europe, it was found that the risk of new-onset asthma was between 2.11 and 3.44 times higher compared with pre-menopausal women[46]. This higher risk of asthma after the menopause is greater in cases of obesity or overweight in women with a natural menopause, and regardless of the weight if the menopause was surgical[47].

It has also been seen that, in menopausal women, compared with the pre-menopausal ones, the fall in lung function is faster, the asthma is more severe, and is less common if they are allergic[12,48]. This could indicate a protective effect of sex hormones, or that the fluctuations in the hormone levels may have a negative impact in the evolution of the asthma. The effect of hormone replacement therapy (HRT) is not clear. On the one hand, it appears that post-menopausal women without asthma previously treated with HRT have a higher incidence of asthma; but in women with previous asthma, the treatment with HRT reduces the symptomatology and the exacerbations[49,50].

CLINICAL PICTURE AND DIAGNOSIS

General approach to diagnosis

The diagnosis of asthma follows the same principles as the general population, based on compatible symptomatology and an objective demonstration of a reversible obstruction of the airway, or bronchial hyper-reactivity in the bronchial challenge test. In this way, both over- and under-diagnosis of asthma in the elderly can be reduced if the objective diagnostic tests are appropriately performed (Table 3)[10,12,51-53].

Diagnostic errors are common in the AAP. Sometimes underdiagnosis may occur when patients have a poor perception of the symptoms, reduced physical activity, accept shortness of breath as something normal, or interpretate the symptomatology as being associated with another illness, or with treatments prescribed for other illnesses[4,12,51]. Furthermore, it is possible that doctors might minimize the symptoms due to considering them being associated with other illnesses, or with age itself (Table 4)[54].

Some studies evaluated the symptoms in relation to lung function measured by spirometry. Compared with younger asthmatics, the AAP show less symptoms associated with asthma, despite having poorer lung function, as well as a lower intensity of shortness of breath for a similar level of obstruction[55]. Furthermore,

Table 3. Clinical and treatment key points of asthma in the elderly

Clinical
The same symptoms as young people
Underdiagnosis
Comorbidities
Poor perception of the symptoms
Treatment
Polypharmacy
Exclusion from clinical trials
Frequent side effects

Table 4. Main reasons for underdiagnosis of asthma in the elderly

Patient's perspective
Poor perception of the symptoms
Reduction in physical activity
Acceptance of the shortness of breath as something normal
Symptomatology being associated with another illness
Doctor's perspective
Minimize the symptoms
Symptoms associated with other illnesses
Symptoms associated with age itself

challenging bronchoconstriction with methacholine, with a greater fall in FEV_1, the AAP refer to less shortness of breath than the younger ones[56].

This poor perception of symptoms also leads to a delay in seeking medical assistance, perhaps being one of the causes of an increase in mortality in this group. In a study with patients that required hospital admission, 65% of the patients over 65 years had more than 14 days with symptoms, whilst in those under 40 years, only 29% had 14 days with symptoms[57].

These factors lead to the underdiagnosis being very common in asthma in AAP, since around 50% of the patients are not diagnosed[58]. In the Salute Respiratoria nell'Anziano (respiratory health in the elderly, SARA) study, which included patients with a mean age of 73 years, only 53% of the asthmatics were correctly diagnosed with asthma, while 19.5% had an erroneous chronic obstructive pulmonary disease (COPD) diagnosis, and another 27% did not have any respiratory diagnosis[59].

Complementary examinations

Regarding the complementary examinations, spirometry with a bronchodilator test is essential in the diagnosis, as in any other asthmatic[1,4]. The underuse of this test contributes to delay and errors in the diagnosis[54].

It is known that the quality of spirometry tests is good in the majority of patients of advanced age. One study evaluating the quality of spirometry in a population aged 65 to 94 years, showed that only 18.2% did not manage to perform a spirometry of good quality. They concluded that age as such is not a limiting factor, but cognitive and functional impairment is[60].

While interpreting the spirometry, it has to be taken into account that the FEV_1/FVC ratio decreases with age, thus it is important to use reference values adequate to this age[4].

If the bronchodilator test (BDT) is negative, a bronchial hyperresponsiveness (BHS) study must be carried out. Challenge tests are safe and

useful in these patients, although they may often be contraindicated, due to poor baseline respiratory function or some comorbidities[10,51,54].

BHS increases with age; therefore, bronchial challenge tests can be less accurate in the elderly[10,51].

The Fractional exhaled Nitric Oxide (FeNO) test is also useful in the AAP, although its evaluation is less clear than in younger patients, as there are less studies. Some authors mention that the FeNO values increase with age, whilst other show the contrary, lower values with higher age[12,54,61].

The forced oscillation technique (FOT) can be used to assess the bronchodilator response and identify alterations in the distal airway. Being an independent effort, it can be useful in this age group, but for the moment its availability is limited[1,11].

The allergy study is important. Although the percentage of atopic individuals is lower than in young patients, it has significant prevalence rates, which vary between 14.7% and 74% of patients[4,10,54].

Other tests can be useful with some specific objectives. The diffusing capacity for carbon monoxide (DLCO) can help to differentiate between asthma and COPD. The CT-scan can identify thickening of the bronchial wall or air entrapment[4,12].

Clusters

Some authors have tried to classify patients into groups, with some homogeneity, defining clusters. Thus, Curto et al.[61] studied 1713 patients in three age groups, less than 65 years, 65-74 years, 75 years or older. They observed that the AAP are more obese, have a poorer FEV_1, a lower FeNO, receive less cycles of systemic corticosteroids (SCS), less doses of inhaled corticosteroids (ICS), and less treatments with monoclonal antibodies (mABs). The most common comorbidities in AAP were gastroesophageal reflux and sleep apnea syndrome[61].

Park et al.[62] carried out a large, prospective, and multicenter study in a Korean population that included 872 patients of 65 years or older, identifying 4 clusters. Cluster 1 was characterized by presenting with symptoms of long-onset and severe obstruction of the airflow; Cluster 2 was mainly made up of women with normal lung function; Cluster 3 contained male smokers with diminished lung function, and Cluster 4 were obese patients with lung function within normal limits. The two most relevant parameters to classify patients were FEV_1 and cumulative smoking history in pack-years.

Comorbidities

Comorbidities are more relevant in the diagnostic approach, since they are associated with more symptoms, a greater limitation of activities, more visits to Emergency Departments, and more hospital admissions[12,63]. In the AAP with asthma, they impact in different ways. There may be interaction between different illnesses, present with similar symptoms that may confuse the diagnosis, including reduced therapeutic compliance due to having multiple treatments, divergences between the

recommendations of different doctors, or pharmacological interactions between different treatments, among other processes[12].

Some variation is also observed at nasosinusal level in the presentation of symptoms in comparison with the younger population. In the AAP, the prevalence and severity of allergic rhinitis, the rate of allergic sensitization and IgE levels are reduced, but the correlation between specific IgE levels and the severity of the symptoms is maintained. In a study performed in Italy on a population of over 65-year-olds, 47.6% had allergic rhinitis, and at least one sensitization in 52.4% of the individuals included in the study[64,65].

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a delayed onset disease, in which age is an important determining factor in its incidence, with a much higher prevalence from 40 years old[66,67].

The clinical presentation of rhinosinusitis in AAP has more loss of smell, but less rhinorrhea and nasal obstruction. It is likely that the anatomical and physiological changes associated with age may underlie these differences in the clinical expression[66].

CRSwNP also shows differences in its evolution depending on age. The AAP have less recurrences after surgery, probably related, at least partly, to the lower cell proliferation capacity in this population[66,68].

One recent meta-analysis showed that, compared with individuals without asthma, the patients with asthma are more likely to have cardiovascular and cerebrovascular comorbidities, obesity, hypertension, diabetes, other metabolic and endocrine diseases, as well as neuropsychiatric, gastrointestinal, and urological diseases and cancer[69].

Depression is particularly significant at this age, affecting 20% of the Western population over 65 years of age. These patients have poor asthma control and more visits to the emergency department. The mechanisms by which the depression worsens the asthma prognosis is not clearly established, but some possibilities are considered, such as a dysfunction of the autonomic nervous system, lower therapeutic compliance, or difficulties in the self-management of the asthma. Given its high prevalence, some specialists advise assessing the possibility of depression with validated scales in all patients with asthma[12].

TREATMENT

The aims of asthma treatment in the AAP are the same as in young people: symptom control, reduction of exacerbations, minimizing adverse effects of the medication as well as the limitations in activities[18,70]. The key points are also the same as in the young individual, objective monitoring: avoiding triggering factors, pharmacological treatment, and patient education[54].

The use of certain medications in the AAP may be dependent on the characteristics of these patients, such as physical and cognitive impairments, financial or daily life difficulties, comorbidities or multiple medication that may produce side effects, and different interactions[1,51,70].

It is especially important to review all the medication that the patients take in each visit, both

prescribed and across the counter, as more than one third of the population between 75 and 85 years-old take at least five medicines. In fact, multiple medication is the most important factor associated with adverse drug reaction and is a risk factor of 30-day hospital readmission in older inpatients discharged home[71,72].

When analyzing the gradual therapeutic dose reduction performed by medical specialists, it is observed that it failed in 41.7% of patients with asthma. Some predictive factors of this failure usually associated with AAP: advanced age, greater baseline severity of the disease, and lower stability time. Furthermore, in the univariate analysis, poor lung function, and having two or more comorbidities, were also associated with higher risk of failure (Table 5)[73]. We must also take into account that the scientific evidence is less solid in this age group, since the inclusion criteria of clinical trials exclude 43% of patients with asthma, rising to 57% in those over 85 years old[74].

Still very relevant in this group is the provision of self-management guidelines, and the implementation of education programs, as it has been observed that they are carried out less often than in the younger population. The characteristics of these patients need to be taken into account, trying to simplify the recommendations, paying attention to aspects such as the print size which may be required to be larger than usual. The education programs should include how to recognize the symptoms of asthma, anti-smoking advice, how to identify triggering factors, and the steps to follow in an exacerbation[10,51].

Influenza and pneumococcal vaccines must be recommended[4]. Recent studies appear to support the advantage of indicating the booster dose of the pertussis (whooping cough) vaccine[75,76].

It is particularly important to choose an easy-to-use inhalation device for these patients, as the technique may be troublesome due to mobility and cognitive difficulties[4,10].

Inhaled corticosteroids (ICS) are the drug of choice for maintenance treatment, with its efficiency being demonstrated in reducing hospitalizations and mortality in AAP with asthma. They appear to be underused in this age group, probably due to certain precautions with their adverse effects and the underdiagnosis of the asthma[10,12]. They may also be less effective in the AAP, as there are more patients with neutrophilic asthma. In fact, in a large retrospective study, it was observed that the therapeutic failure of ICS in asthma increases with age[77]. They can produce dysphonia or oral candidiasis, which is reduced with mouthwashes after their use. In patients treated with high doses of ICS, and especially in women, the risk of osteoporosis must be monitored, and advise prevention of this complication. A risk of glaucoma and cataracts has also been described. In order to avoid side effects, it may be effective to use molecules with a lower bio-availability, and with the lowest dose necessary[10,12,51]. Nasal ICS are effective and safe for the treatment of rhinitis[12].

The use of beta-agonists follows the same criteria as in a younger population, although the evidence is weaker due to there being few studies in this age group[12]. The bronchodilator response could be lower since age can diminish the density, response, and affinity

Table 5. Usual treatments and side effects

Drug	Side effects	Alternative treatment
Non-cardioselective beta blockers	Bronchospasm	Cardio-selective beta-blockers
Topic beta blockers (eye drops)	Asthma exacerbations	
Beta 2 agonists	Trembling, tachycardia, decrease serum potassium, prolonged QT interval dose-dependent	
Non-steroidal anti-inflammatory drugs	Asthma exacerbations	Paracetamol
Angiotensin converting enzyme inhibitors	Cough	Angiotensin-2 blockers
Anticholinergics	Dry mouth, blurred vision, dry eyes, constipation, urinary retention, dizziness, postural hypotension, confusion, heart rhythm disturbance, elevated intraocular pressure	
Theophylline	Atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, seizure	
Systemic corticosteroids	Decreased bone density, cataracts, glaucoma, muscle weakness, diabetes, hypertension, psychiatric disturbances	Inhaled steroids
Inhaled corticosteroids	Hoarse or croaky voice, cough, oral candidiasis	Use spacer/valved holding chamber and metered dose inhaler

of the beta-agonist receptors[10]. Additionally, it is necessary to take certain special precautions with the side effects such as tachycardia, tremor, reduction in serum potassium and prolongation of the QT interval, which can be more intense than in a young population[10,51,78].

Long-acting anti-muscarinic agents (LAMA) are effective as complimentary treatment in asthma, although the evidence is weak due to the known lack of studies in this age group. Some publications suggest that the AAP may have a better bronchodilator response with anticholinergics than with beta-agonists, due to the lower response of beta-2 receptors[12]. They may be added to the ICS when there is concern about the safety of the beta-agonists, or to a combination of ICS with long-acting beta agonists (LABA), since it has been shown to reduce exacerbations in a study that includes patients up to 75 years of age[79]. The side effects of the antimuscarinics are rare when used in an inhaler[68]. They can produce dry mouth, urinary retention, constipation, and an increase in intraocular pressure, so for this reason it will be necessary to particularly assess the comorbidities of these patients, since pathologies such as glaucoma or prostatic hypertrophy are more common at this age[51].

Leukotriene receptor antagonists (LRA) are safe and may be used as second line anti-inflammatories. It has been demonstrated that adding LRA to patients treated with low doses of ICS in AAP with asthma reduces exacerbations in comparison with those treated with ICS only. Furthermore, its ease of use and its oral administration may favor the compliance with the treatment. Some adverse effects have been reported, such as gastrointestinal

problems, sleep disorders, and neuropsychiatric events[10,78,80,81].

Theophylline must be avoided, if possible, in AAP. Its narrow therapeutic margin, and the interaction with several drugs increases the risk of side effects[51].

The systemic corticosteroids (SCS) are used with the same indications as in younger patients, although special attention must be paid to the side effects, since the AAP may have illnesses that are aggravated with the use of these drugs, such as osteoporosis, cataracts, psychiatric disturbances, or glucose metabolism[51,82]. Furthermore, they may be less effective since there are more patients with neutrophilic asthma[10,12].

One aspect to take into account, is the accumulated dose of systemic corticosteroids, since the side effects of corticosteroids are clearly related to the administered dose and the duration of the treatment. Cumulative lifetime SCS exposure was associated with a higher prevalence of frailty, muscle weakness, osteoporosis, pneumonia, cardio-/cerebrovascular diseases, cataracts, sleep apnea, renal impairment, depression/anxiety, type- 2 diabetes, and obesity[83-86].

If antihistamines are used, it must be remembered that they may produce blurred vision, confusion, constipation or dry mouth[51].

The monoclonal antibodies (mABs) available for the treatment of asthma have demonstrated their efficacy and safety, both in clinical trials and in studies of usual clinical practice. With the limitation of the scant availability of studies in these patients, it is does not seem that age is a factor that may influence the results[41,87,88].

Allergen immunotherapy (AIT) can be used in the AAP, although their indications and contraindications have not been specifically defined. The European Academy of Allergy and Clinical Immunology (EAACI) does not establish any upper age limit from which this treatment can be used, since the immune system can be modulated from infancy up to advanced ages[65,89]. There is evidence that demonstrates the effectivity of AIT in the AAP, reducing the levels of specific IgE, the symptoms, and the need for other treatments, as well as preventing the progression of allergic rhinitis to asthma[65,89-91].

In the AAP, it is particularly important to consider the comorbidities and the contraindications. AIT is contraindicated in patients with uncontrolled asthma or with significant cardiovascular disease, and it must be administered with caution in patients treated with beta-blockers or ACEIs[65,89].

The incidence of systemic reactions in relation to subcutaneous immunotherapy (SCIT) is 0.1% and is lower in sublingual immunotherapy (SLIT). Given this better safety profile and the possibility that it may be administered at home, the use of SLIT is recommended in the AAP; although it must be individualized as the compliance with SLIT is less than with SCIT[65.89].

The management of comorbidities is particularly complex in this population group, since they are more frequent and increase mortality, as well as the exacerbations, the hospital admissions, visits to the emergency department,

reduce therapeutic compliance and the quality of life[18]. Multimorbidity, understood as the presence of two or more illnesses in the same patient, affects around 62% of individuals between 65-74 years, and 81.5% for those over 85 years[92].

Given that comorbidity is common in the AAP, the treatments of these illnesses will also be common[13,93,94]. Due to their common use, including topical use, the beta-blockers are of particular importance, as are the non-steroidal anti-inflammatory drugs (NSAID's), and angiotensin converting enzyme inhibitors (ACEI). The use of cardioselective beta-blockers may be safe in well-controlled asthmatics[10,51].

CONCLUSION

In conclusion, asthma exists in AAP. The incidence of new cases is relatively high and their management, both diagnostic and therapeutic, is similar to younger patients, considering some peculiarities of this population group.

DISCLOSURES

The authors have nothing to disclose.

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