

Asthma pathogenesis, diagnosis, and management in the elderly

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ABSTRACT

Background: Due to the aging population, there is an increase in the number of elderly patients with asthma. Although signs and symptoms are similar to those in younger patients, diagnosis can be challenging due to presence of coexisting conditions in this population.

Objectives: The purpose of this review was to highlight the challenges with regards to diagnosis, management, the high rates of medical costs and mortality in elderly asthmatics.

Methods and Results: Scientific literature regarding asthma in the elderly population was reviewed. When compared to younger patients, elderly asthmatics have different drug responses, higher rates of bronchial hyper reactivity, more severe phenotype, and lower prevalence of atopy. In addition, there are issues with the adverse effects of asthma medications, use of proper inhaler technique and compliance.

Conclusion: There is an unmet need for research in elderly patients with asthma, specifically to facilitate diagnosis, and to investigate therapeutic strategies to improve quality of life in this population.

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Worldwide, rapid increases in the elderly have led to estimates that the number of elderly individuals may double by 2030.¹ Census data from 2010 indicate that the elderly population (>65 years of age) account for 13% of the U.S. population, or 40.3 million people.² Estimates are that this age group will account for 25% of the population by 2050, or roughly 86 million people.³ Healthcare providers are currently not equipped to handle this challenge.⁴ Asthma prevalence in the elderly patient is difficult to determine because of underdiagnosis due to patient underreporting of asthma symptoms or of misdiagnosis as chronic obstructive pulmonary disease (COPD).⁵ According to the National Health Interview Survey data, the annual prevalence of self-reported asthma in individuals who are >65 years old is 6.8%.⁶ Asthma was once considered primarily a developmental disease of childhood; however, several studies report that the lifetime prevalence is high in the elderly patient, close to 13% compared with roughly 14% in children of ages <18 years old and 7.5% in adults ages 18–74 years.^{6–21} The burden of medical costs (direct and indirect), hospitaliza-

tion, and mortality is high compared with younger age groups.^{3,6,22–25}

ROLE OF EPIGENETICS

Epigenetics has recently been added to the traditional view of disease susceptibility to account for the influence of environmental factors and aging on the genomic blueprint.³ Epigenetics can be defined as chromatin and DNA modifications that are heritable through cell division without altering DNA sequences.^{26,27} Epigenetics is the interaction of genotype and the environment that generates a particular phenotype and explains differences among cells, tissues, and organ despite identical genetic information.³ For example, identical twins share the same genome yet have different life spans and disease susceptibilities.²⁸

Alterations in epigenetic machinery are associated with diseases such as cancer and autoimmunity. Specifically, global DNA hypomethylation seems to be a feature of aging cells and tissues, and is observed in age-related diseases, including cancer, Alzheimer's disease, and atherosclerosis.²⁹ Also, age-associated hypermethylation of certain regions, such as tumor suppressor genes, may play a role in cancer development.^{1,26} Asthma is a heterogeneous disease with a strong environmental component.³⁰ There is recent evidence that environmentally induced epigenetic changes can contribute to varying asthma phenotypes.³ Much remains unknown about the epigenetics of asthma and the role that epigenetics plays in the inherent differences between elderly patients with asthma and younger cohorts.^{3,30}

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ROLE OF ALLERGEN SENSITIZATION

There is a known link between the early presence of atopy and the later development of asthma.^{31,32} The prevalence of atopic conditions has increased in general over the past decades, which may increase the burden of asthma in elderly patients. The role of atopy and asthma in older subjects, unlike in children and young adults, is not completely understood. There is a decline in the innate and adaptive immunity with aging,^{33,34} but the effect of these changes in elderly patients remains unclear. Serum immunoglobulin E (IgE) and antigen specific IgE sensitization decline with age. The National Health and Nutrition Examination Survey 2005–2006³⁵ and Tucson Epidemiologic Study³⁶ reported that IgE peaks by 20 years old and is lowest after 70 years old.

For many years, asthma in older patients was characterized as nonallergic or intrinsic.³⁷ However, there is emerging evidence that atopy is not uncommon in elderly patients with asthma. Evidence that supports the role of allergens as a cause of asthma symptoms in elderly patients has been conflicting. Results of two studies indicate only small percentages of elderly patients with asthma have allergic causes.^{38,39} Results of another study indicated that the prevalence of allergen sensitization is high, which supports IgE-mediated mechanisms in elderly asthmatics.⁴⁰ Furthermore, the rate of allergen sensitization is higher in older patients with asthma compared with age-matched controls without asthma.^{41,42} Two studies of older (>65 years) patients with asthma from U.S. inner-city populations found that 60% had at least one detectable allergen-specific IgE antibody,⁴⁰ and 41% were sensitized to at least one antigen.⁴³ The most common aeroallergens in older patients with asthma include cat,⁴⁴ dust mites,^{42,43} and cockroach.⁴⁰ However, the importance of this sensitization and its effect on disease severity is still not clear.

ROLE OF INFECTIONS

Asthma exacerbations in children are commonly associated with rhinovirus upper respiratory tract infections (URI).⁴⁵ Viral URIs might be a precipitating factor for elderly patients with asthma, although studies regarding the specific pathogen are lacking. A prospective study, by Beasley *et al.*,⁴⁶ showed that viral respiratory tract infections may cause exacerbations of asthma in adults, which can be severe. Falsey *et al.*,⁴⁷ in a prospective study, identified respiratory syncytial virus infections during four consecutive winters in elderly patients, in adults at high risk, and in patients who are hospitalized with acute cardiopulmonary conditions. Respiratory syncytial virus infection accounted for 11% of hospitalizations for pneumonia, 11% for COPD, 5% for congestive heart failure, and 7%

for asthma during the study period. Thus, viral URIs are precipitating factors for asthma exacerbations in elderly patients.

Vaccination in the elderly patients can lead to sustained immune responses and prevent significant morbidity and mortality associated with infectious diseases. Influenza vaccine is shown to be protective in children in preventing asthma exacerbations, but the efficacy data in the elderly are lacking.⁴⁸ The U.S. Advisory Committee on Immunization Practices recommends that all adults ages ≥ 65 years of age should receive both pneumococcal conjugate vaccine-13 and pneumococcal polysaccharide vaccine-23 to prevent the development of pneumonia⁴⁹ and asthma exacerbations.

DIAGNOSIS

An asthma diagnosis can be challenging in the elderly patient. Symptoms of asthma may be misinterpreted as due to other common chronic diseases, including COPD or cardiac disease. Sometimes the asthma-induced limitations are attributed to normal aging. Lung function declines with age, more so in men than in women.⁵⁰ Even in normal elderly individuals, forced expiratory volume in the first second of expiration (FEV₁) to forced vital capacity is lower, which may be indicative of obstruction. The elderly patient thus may be misdiagnosed as having COPD, which results in asthma underdiagnosis and undertreatment.⁵¹ Personal and/or family history of atopy with onset of asthma symptoms in early childhood is more likely indicative of asthma compared with a history of tobacco use and adult onset of symptoms that are more indicative of COPD. Peripheral and/or sputum eosinophilia, elevated total serum IgE, and/or elevated fractional exhaled nitric oxide (FE_{NO}) are biomarkers supportive of asthma.⁴³

Two phenotypes of asthma in the elderly have been previously described: longstanding asthma, which begins in childhood and is commonly associated with atopy, and late onset asthma, which begins after middle age and is less likely to be associated with atopy.^{51,52} Reversibility of airflow obstruction (>12%) with bronchodilators, helps differentiate asthma from COPD. However, this diagnosis can be difficult in the elderly patient.^{3,53} A European study, the Respiratory Health in the Elderly,⁵⁴ found that only 53% of elderly patients with asthma had a correct diagnosis.

Spirometry is an essential tool for diagnosis. FEV₁ increases of at least 12% after short-acting β agonist inhalation is key in the diagnosis. Because of poor physical functioning and cognition, it may be difficult to obtain meaningful spirometry in 10–20% of elderly patients.^{55,56} Lung function in patients with COPD shows increased lung volume and reduced diffusing

capacity. These findings, coupled with reduced FEV₁ to <60% predicted, are suggestive of COPD rather than of asthma in the elderly patient.⁵² High-resolution computed tomography of the chest is more sensitive to detect emphysematous changes in patients with COPD, which may be absent on chest radiographs. The prevalence of irreversible airway obstruction is speculated to be high in elderly patients with asthma. Expert panel report 3 (EPR-3) indicates that a 2-week trial with systemic steroids, followed by repeated spirometry, will determine the patient's "personal best" by reversing severe asthmatic obstruction.⁵⁷

Airway hyperresponsiveness (AHR) to nonspecific stimuli is a hallmark of asthma and is responsible for most clinical features of this disease.⁵⁸ The prevalence of AHR has been proposed to increase with age.^{59,60} A study indicated that, despite comparable lung functions, the airways of elderly patients with asthma are more reactive than those of young patients with asthma when tested by methacholine,⁶¹ which implies that elderly patients with asthma are at higher risk for airway closure. Hopp *et al.*⁶² showed that the area under the flow volume dose response curve was smaller (higher responsiveness) in subjects 67–86 years old than that in a younger group. In another study, the rate of AHR was 11.2% in older adults (45–74 years old) and 6.7% in younger adults (30–44 years old).⁶³ Because the perception of symptoms may be blunted in the elderly patient, assessment of AHR may be considered as an additional diagnostic tool in the workup of subjects at risk, such as those with long-term smoking exposure and/or documented atopy.⁵⁹

Measurement of Allergic Airway Inflammation by Exhaled Breath Nitric Oxide

The diagnosis of asthma relies on an assessment of clinical symptoms and the presence of reversible airway obstruction.^{57,64} However, airway inflammation can be present in patients with well-controlled asthma and with normal spirometry, which indicates that spirometry may not be sensitive enough to detect airway inflammation. AHR, an exaggerated bronchoconstrictor response to inhaled stimuli, is a key feature of asthma and relates closely to the severity and frequency of symptoms, and the need for treatment.⁶⁵ Assessment of AHR through provocation tests is time consuming and costly, and bears a small risk of inducing severe bronchospasm.⁶⁶ Alternatively, the FE_{NO} measurement is simple and noninvasive, and may represent a safer method to evaluate eosinophilic airway inflammation. With portable electrochemical analyzers,^{67–72} FE_{NO} can be assessed readily in research or in clinical practice.^{73,74}

FE_{NO} is increased in atopic asthma, is reduced by corticosteroid treatment, and is not modulated by

bronchodilator therapy.⁷³ A correlation between AHR and FE_{NO} has been described.^{75–77} An American Thoracic Society (ATS) clinical practice guideline⁷³ proposes cutoff points for interpretation: (1) FENO < 25 ppb (<20 ppb in children), eosinophilic inflammation and responsiveness to inhaled corticosteroids (ICS) is unlikely; (2) FE_{NO} > 50 ppb (>35 ppb in children), eosinophilic inflammation is likely, responsiveness to ICS is likely; but (3) FE_{NO} values between 25 and 50 ppb (20 and 35 ppb in children) must be interpreted cautiously within the clinical context.

There are several confounding factors that affect FE_{NO}, including age, which seems to be important in children,⁷⁸ with less agreement across studies regarding the influence of age in adults, or the influence of sex and height in the elderly population. Age is related to FE_{NO} among subjects who are <18 years old, perhaps due to increases in the airway mucosal surface area that produces nitric oxide.⁷⁹ In a large study, Olin *et al.*⁸⁰ identified age and height as affecting FE_{NO} but found no difference between male and female patients. A cross-sectional analysis of the National Health and Nutrition Examination Survey from 2007–2010 showed that, overall, FE_{NO} increased with increasing age ($p < 0.001$).⁸¹ Unfortunately, there are no published data specifically on FE_{NO} in the elderly (>65 years old). Nevertheless, FE_{NO} may be useful in evaluation of eosinophilic airway inflammation in the elderly.

MANAGEMENT

Asthma management is similar in young and elderly patients with asthma. The National Institutes for Health and Global Initiative for Asthma is used for the management of asthma in the elderly patient.^{82,83} The primary goals are to achieve optimal asthma control and prevent exacerbations.⁸⁴ More than half of adults with asthma report one or more coexisting medical conditions, with higher rates in women.⁸⁵ In the United States, 36% of adults >60 years use five or more prescription medications daily.⁸⁶ One study of older adults with asthma found that some patients with coexisting cardiac disease have been instructed to try medications for both conditions simultaneously and/or sequentially during periods of dyspnea.⁸⁷ In the elderly patient with multiple comorbidities, medication costs can increase and some patients may receive suboptimal treatment because of lower prioritization.⁸⁸

Common comorbidities in elderly patients include gastroesophageal reflux disease (GERD), diabetes mellitus, chronic rhinosinusitis with or without nasal polyps, obesity, and congestive heart failure.⁸⁹ Topical ocular or systemic β -blockers, which are commonly prescribed in this population, can potentially worsen bronchospasm, and preferentially using cardioselective

tive β -blockers when indicated has been suggested to limit adverse pulmonary effects.^{90–92} GERD symptoms can mimic and sometimes exacerbate asthma.³ Typical GERD symptoms, such as heartburn, dysphagia, or odynophagia may not be the presenting symptom in elderly patients with asthma.^{3,93} In most cases, asthma is associated with nasal disease (nonallergic or allergic). Nonallergic rhinitis affects a large number of the elderly patients, and, in some cases, it can coexist with allergic rhinitis but may be difficult to diagnosis due to a lack of specific diagnostic criteria.⁹⁴ Treatment of upper airway disease (both allergic and nonallergic rhinitis) is important in asthma control.⁹⁵ Treatment of other comorbidities, such as weight loss in patients who are obese and have asthma, and treatment of GERD will help to control their asthma.

Because symptoms of airway obstruction are often underreported, use of spirometry and/or FE_{NO} may be appropriate in elderly patients with asthma as a baseline assessment.^{82,96,97} For acute symptom relief, β -adrenergic agonist remains the criterion standard of treatment. However, these agents can cause adverse effects in elderly patients with asthma such as tremors, tachycardia, or dysrhythmias.⁹⁸ ICS are the cornerstone of asthma management, and there is strong evidence that ICS are effective and safe; unfortunately, most of these studies did not include elderly subjects. There have been reports of underuse of anti-inflammatory treatment in elderly patients.⁹⁹

There are different delivery systems available to generate therapeutic aerosols in the treatment of asthma, including dry powder inhalers (DPI), metered-dose inhalers (MDI), and nebulizers.¹⁰⁰ MDIs are more convenient and portable, and do not require drug preparation but do require patient coordination (or are technique dependent). Many elderly patients cannot inhale these effectively and thus may not deliver sufficient concentrations to peripheral airways, with lung deposition between 10 and 40% of the dose. The addition of a spacer can help address this. Many patients find DPIs easier to use because it is breath actuated, requires less patient coordination, and is convenient and portable. Some patients may not inhale rapidly enough to aerosolize the powder because moderate-to-high inspiratory flow is required. Inadequate flow can cause high pharyngeal deposition, which results in local adverse effects. In such cases, a nebulizer might be necessary.

Nebulizer systems do not require patient coordination but are typically less portable than MDIs and DPIs, require more time for delivery, are less efficient than other devices (dead volume loss), require cleaning, and, in certain circumstances, can be more expensive.^{52,101} Regardless of the delivery device, careful instruction is essential, and, at each visit, the patient technique must be reviewed. ICS have some systemic absorption, with the potential for adverse effects, espe-

cially if used for extended periods in high doses. Local adverse effects, such as dysphonia and oral candidiasis, can be minimized by spacer use with MDIs. Prolonged ICS use in the elderly patient increases the risk of cataracts, open-angle glaucoma, and increased intraocular pressure.^{102–104} For these reasons, some experts recommend the lowest effective dose therapy to control symptoms. Long-acting β_2 -adrenergic agonists (LABA) can be used in conjunction with ICS in patients with moderate-to-severe asthma.

Results of the Salmeterol Multicenter Asthma Research Trial¹⁰⁵ indicate that African American patients who received LABA had an increased risk of respiratory-related death or life-threatening events. However, subsequent studies allayed some concerns regarding LABA safety when combined with ICS.^{106,107} Patients on long-term high-dose ICS with or without LABA may be at increased risk for osteopenia and osteoporosis. Women who were postmenopausal and were treated with an ICS had significantly lower bone mineral density than age-matched controls.¹⁰⁸ A large study of elderly individuals with either asthma or COPD (mean age, 81 years) who denied previous use of oral corticosteroids found a dose-dependent positive association for fracture risk with the use of ICS.¹⁰⁹ Bone mineral density studies and ophthalmologic examination in the elderly patient on high-dose ICS should be conducted periodically. Long-term oral steroid use increases the risk for cataracts, osteoporosis, and muscle weakness, and should be avoided.³

Leukotriene antagonists, because of their safety profile, can be considered as second-line anti-inflammatory treatment after ICS or as add-on therapy.^{5,98,110} Korenblat *et al.*⁹⁸ found that zafirlukast therapy was effective and well tolerated by adolescents, adults, and elderly patients with asthma, but pulmonary function and symptom improvement was less dramatic in the elderly patient than in adolescents and adults. A more-recent randomized, open-label, parallel-designed trial showed that the addition of montelukast to low-dose ICS leads to fewer asthma exacerbations in elderly patients with asthma than ICS monotherapy.¹¹¹ Anticholinergics can be considered in elderly patients with asthma when there is concern of adverse effects due to β -agonists. Ipratropium bromide (a short-acting bronchodilator) and tiotropium (a long-acting bronchodilator) have good safety profiles and should be considered as add-on therapy to ICS.¹¹² In poorly controlled asthma despite treatment with ICS and LABAs, adding tiotropium reduced the risk of asthma exacerbations that required systemic steroids.¹¹³

Allergen immunotherapy is effective in treating allergic asthma in patients with unavoidable allergen exposure and should be considered in those situations.¹¹⁴ There are no controlled trials of allergen immunotherapy in the elderly. An open-label study of

patients ages >54 years on allergen immunotherapy reported a reduction in their symptoms.¹¹⁵ Two randomized, double-blind, placebo controlled studies evaluated the use of sublingual immunotherapy, specifically to grass pollen and house-dust mite, in patients of >60 years old.^{116,117} Both studies showed statistically significant clinical improvement with reduction in nasal symptom score and medication use.

Omalizumab, a monoclonal anti-IgE antibody is approved for the treatment of moderate-to-severe allergic asthma. Omalizumab is effective in decreasing asthma exacerbations, improving quality of life, and reducing ICS use.^{118–120} Bousquet *et al.*¹²¹ found that omalizumab reduced asthma exacerbations and emergency medical visits in patients (ages, 12–79 years) with severe persistent asthma; however, it did not reach statistical significance in the subgroup of elderly patients with asthma (>65 years old).¹²¹ “Pooled analysis” from five studies showed that omalizumab treatment resulted in improvement in asthma exacerbations in older patients (≥50 years old).¹²²

There have been attempts to categorize asthma into different phenotypes. One of the most prominent phenotypes is characterized by eosinophilic airway inflammation, despite the use of high-dose anti-inflammatory treatment, and often requires frequent bursts or even daily corticosteroids.^{123–125} Anti-interleukin 5 humanized monoclonal antibody was approved by the U.S. Food and Drug Administration for treatment of severe, eosinophilic asthma. Two multicenter, randomized, double-blind, placebo controlled studies (DREAM¹²⁶ and MENSA¹²⁷) showed reduction in asthma exacerbations with the use of anti-interleukin 5 in those ages 12–74 years and 12–82 years, respectively, and could be an add-on treatment for elderly patients with asthma and with an eosinophilic phenotype.

CONCLUSION

Asthma in elderly patients is common but remains underdiagnosed and undertreated. This entity should be considered a distinct phenotype with different characteristics than adult asthma, which can potentially impact diagnosis, assessment, and management in this population. Diagnosis of asthma in the elderly patient depends on the same clinical findings and diagnostic testing used in younger populations; however, interpretation of these data can be difficult. In addition, comorbid conditions that are commonly associated with polypharmacotherapy may modify pharmacokinetics of asthma medications, which can have significant impact on treatment outcomes. The Expert Panel Report 3 (EPR3),⁸² presents asthma guidelines for elderly patients and addresses some key issues, particularly adverse effects related to medications. Nevertheless, large, longitudinal studies are needed to

determine the effects of aging on the function of the respiratory system. To differentiate asthma from other obstructive diseases, better diagnostic tools and age-appropriate biomarkers are needed. With the expectant increase in the aging population, asthma in this group will present new challenges. Research should focus on strategies to improve diagnosis and management for this vulnerable population and to provide better quality of life.

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