

Asthma in the geriatric population

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ABSTRACT

Asthma is associated with significant morbidity and mortality in the geriatric population. Despite the rising incidence of asthma in people >65 years of age, the diagnosis is frequently missed in this population. Factors that contribute to this include respiratory changes caused by aging, immunosenescence, lack of symptoms, polypharmacy, clinician unawareness, and lack of evidence-based guidelines for diagnosis and management that target this population. This literature review addresses the current state of research in this area. Age-related changes influence the pathophysiology and role of allergy in elderly asthmatic patients. Specific obstacles encountered in caring for these patients are discussed. Asthma in the elderly and younger population are compared. We conclude with a broad set of goals to guide future management driven by a multidiscipline approach.

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The fastest growing segment of the population consists of people >65 years of age.¹ The presence of multiple comorbidities and age-related physiological changes influence the clinical presentation, diagnosis, and management of many diseases. The estimated prevalence of asthma in adults >65 years old is 4–13%.² With the current rise in the elderly population, there is a disproportional increase of asthma in this population.³ Hospitalizations and mortality rates related to asthma are highest in this age group.⁴ Clinicians generally do not consider asthma as a primary diagnosis in this population. Elderly patients tend to have more than one pulmonary disease, which further complicates the diagnosis and management.⁵

Asthma is a treatable disease with significant morbidity; thus, clinician awareness is paramount. Acute respiratory symptoms are one of the most common reasons for elderly people to seek medical attention. Several problems, unique to the elderly asthmatic patients, are particularly challenging. These include delayed appearance of symptoms, the presence of multiple comorbidities, polypharmacy, lack of treatment response, and physiological changes in the respiratory and immune systems. Table 1 compares asthma in the younger and older populations. A multidiscipline approach is required for better management. There is a current movement into translational research. Because of these challenges, the National Institute on Aging sponsored a “Workshop on Asthma in the Elderly” in Herndon, VA, on September 8–9, 2008.²

PROCESS OF AGING

Aging is a natural process associated with cellular changes causing increased vulnerability to stressors and disease. This process is independent of the multiple comorbidities frequently observed. Many gaps exist between the process and the observed phenotype. It appears that the total number of replications is a most important factor contributing to cellular senescence. At the phenotypic level, aging is associated with the concept of frailty. Frailty is a state of decreased physiological reserves with increased risk of morbidity and mortality. A model of frailty has been developed by Fried *et al.*⁶ This frailty index has been validated by observational studies.⁷ Frailty was considered present with three or more of the following criteria: unintentional weight loss of 10 lb in a year, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity. The phenotypic manifestations include sarcopenia, osteopenia, anemia, and cognitive decline. Consequences include increased hospitalizations, falls, dementia, and mortality. Frailty has been associated with a decreased cellular immune response and elevated inflammatory markers.⁸ Markers of inflammation and oxidative stress are currently being investigated for their diagnostic and prognostic value.⁹ Current gaps in our knowledge include how these molecular level changes are related to the frailty phenotype. This knowledge can aid in the treatment of disease.

AGING AND THE IMMUNE SYSTEM

Aging is associated with a progressive complex remodeling of the immune system known as immunosenescence. Although much of the evidence on the mechanisms of immunosenescence comes from mouse models, it is well established that age is associated with impaired adaptive immunity in humans. This contributes to age-related risks for autoimmune reactions,

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Table 1 Comparison of asthma in younger and older populations

Factor	Younger	Older	Reference
Hospitalization	Less frequent	More frequent	4
Inflammatory cells	Eosinophils	Neutrophils	10
Immune system	Adaptive	Innate	19 and 36
Role of atopy	Common	Uncommon	32 and 85
Role of vitamin D	Stronger evidence	Less evidence	94 and 95
Exacerbation triggers	Respiratory infection and allergens	Respiratory infection, allergens, GERD, congestive heart, failure, and medication	2
Reporting of symptoms	More likely	Less likely	3
Disease course	Detected at earlier stages and followed by higher remissions	Detected at later stages, more progressive, and less remissions	79 and 80
Disease control	As-need inhaled bronchodilator more likely to be adequate	Continuous treatment more likely needed	79
Differential diagnosis	Smaller	Larger	65, 74, 96, and 97
Response to β -agonist	Higher	Lower	56
Obstruction reversibility	More complete	Less complete	11
Treatment compliance	More likely	Less likely	77
Mortality rate	Lower	Higher	4 and 59

GERD = gastroesophageal reflux disease.

malignancy, poor wound healing, and an impaired response to infection. The most dramatic changes are observed with cellular immunity. There is a general shift from a stimulatory to a suppressive cytokine microenvironment.¹⁰ T cells are less responsive to antigens and mitogens.¹¹ This leads to T-cell anergy.¹² There are decreased naïve cells, increased memory T cells, increased regulatory T-cells cells, and lower IL-2 receptiveness.¹³ Similar changes take place for B cells.¹⁴ Th17 cells are a group of effector T cells that secrete proinflammatory cytokines under the influence of IL-6, which is known to increase with aging.¹¹ Mouse models have suggested that these cells are important in airway inflammation during asthma exacerbations.¹⁵

For the innate immune system, there is evidence that age-related changes to dendritic cells leads to an increased risk of T-cell-mediated autoimmunity.¹⁶ Phagocytic cells use Toll-like receptor-mediated signaling pathways to recognize and process pathogens. *In vitro* studies have shown that these receptors are down-regulated in aged cells.^{17,18} Monocytes and macrophages are decreased in the bronchoalveolar lavage fluid of elderly asthmatic patients and have diminished cytotoxicity. There is also decreased ability to down-regulate inflammation. This promotes chronic, nonspecific inflammation.¹⁹ Biomarkers remain a promising tool to predict the level of immune competence and mortality risk in the elderly population.¹²

AGING AND THE RESPIRATORY SYSTEM

Age-related changes in respiratory physiology include reductions in functional residual capacity, expiratory flow rate, diffusion capacity, and a slight decline in arterial Po_2 .²⁰ Mild hypoxia is common whereas hypercapnia is not observed. The spirometry determined forced expiratory volume at 1 second (FEV_1) declines continuously with age. Diminished elastic recoil may contribute to this.²¹ A significant reduction in FEV_1 predicts increased mortality.²² Alveolar dead space increases and leads to higher residual volume. There is reduction in the alveolar surface area causing hyperinflation without alveolar destruction or changes in total lung capacity. Age-associated musculoskeletal changes can result in chest wall and thoracic spine deformities. The net effect of changes is an overall decreased compliance and increased work of breathing.²³ The rate of decline is variable.²⁴ Despite these ventilation-perfusion mismatches adequate gas exchange is normally observed throughout life.

There is an age-related decrease in the ventilation response to both hypoxia and hypercapnia. The mechanism likely involves changes in the nervous system.²⁵ The clinical significance is a lack of dyspnea despite significant changes in blood gases.²⁶ This leads to reduced awareness of worsening airflow obstruction. A reduction in the usual activity may be an early warning

sign that deserves further evaluation before the subjective sensation of dyspnea occurs.²⁷ The use of the 6-minute walk test has shown to be helpful.²⁸

ASTHMA AND THE ELDERLY

Pathophysiology

The clinical manifestations of asthma include episodic wheezing, cough, and dyspnea. The underlying pathophysiology involves airway obstruction due to a hyperactive inflammatory response.²⁹ Inflammatory mediators trigger bronchospasm, airway edema, smooth muscle hyperplasia, and mucus secretion. Exhalation is limited, resulting in air trapping and lung hyperinflation. Breathing at high lung volumes is an important cause of dyspnea. Over time, chronic inflammation leads to airway remodeling, resulting in permanent basement membrane thickening, fibrosis, and increased number of mucus-secreting cells.³⁰ Long-standing asthma increases the risk for fixed obstruction.³¹ This underscores the importance of good control early in the disease course with a goal of reducing the number of exacerbations.

Asthma in adults can be categorized based on neutrophilia, eosinophilia, IgE levels, associated atopy, age of onset, and symptom severity.³² These phenotypes are important for predicting prognosis and to develop targeted therapies.³³ Late-onset asthma, where symptoms began after the age of 40 years, is associated with lack of atopy, lack of familial clustering, and neutrophilic inflammation. On the other hand, early onset asthma that extends into adulthood is associated with atopy. A higher neutrophilic response was observed in the bronchoalveolar lavage fluid in elderly asthmatic patients.¹⁰ Although the role that neutrophil predominance plays in disease severity is not well understood, this phenotype is less reversible.³⁴ Long-standing asthma may lead to chronic persistent airflow obstruction mimicking chronic obstructive pulmonary disease (COPD), complicating the diagnosis in the elderly population.³⁵

Immunosenescence likely alters the pathogenesis of asthma. Long-standing asthma is associated with activation of the innate immune system.³⁶ One study, using mouse models, showed that chronic inflammation of the lungs is driven by natural killer cells and macrophages, suggesting the importance of the innate immune system.³⁷ Neutrophil-predominant inflammation increases with age and is generally more severe and difficult to control.³⁸ Chronic exposure to environmental pollution and cigarette smoke also plays a role.³ The effect of T-cell immunosenescence on the pathophysiology of asthma was investigated using T cells from healthy elderly and asthmatic patients.³⁹ The pattern of decreased T-regulatory cells associated with asthma was similar to that found in the younger pop-

ulation but the magnitude of this difference is lower in the elderly population.³⁹ This study showed that despite the known decline in lymphocyte function with aging, the healthy elderly group responded in the same way as in younger population. Phenotypical and pathophysiological differences between younger and older populations with asthma will likely play a larger role in managing these patients in the future.^{40,41} Table 1 is a general comparison of asthma in the elderly to younger population.

Role of Allergy

Early onset asthma is defined as asthma from childhood that persists into adulthood. These patients have a greater likelihood of previous allergic disease and genetic predisposition.^{2,42} Allergen-triggered asthma symptoms tend to diminish with aging as is shown by the decreased reaction to skin testing. Total IgE is also decreased. One observation study showed that a qualitative serologic assay is a valuable tool for the diagnosis of allergic sensitization.^{43,44} Despite the decline in allergic reactions of the elderly population, allergy should be considered particularly in those with rhinitis.⁴⁵ It appears that a history of allergic asthma reactions may trigger changes in lung physiology that progress to adulthood despite the lack of allergic response. One cross-sectional study showed that a history of atopy was the strongest predictor of asthma.⁴⁶ Age-related changes such as atrophy of connective tissue can lead to weakening of septal cartilage and a reduced blood flow to nasal tissues.⁴⁷ These changes can cause increased nasal congestion predisposing the patient to rhinitis or complications of existing allergies.^{48–50} Chronic rhinosinusitis is an independent risk factor for more severe asthma. It can trigger biofilm formation, which supports a chronic inflammatory state and heightened asthmatic response.⁵¹ One cross-sectional study observed that elderly asthmatic patients were more likely to have childhood respiratory problems, hay fever, chronic bronchitis, and daytime sleepiness.⁵ Another retrospective observational study showed that elderly patients with severe atopic asthma can have a significant positive response to omalizumab.⁵²

Clinical Diagnosis

Symptoms have been shown to underestimate the severity of asthma in the elderly population.⁵³ Current guidelines need to be adjusted to account for aging. Spirometry is less reliable in elderly patients because it is usually extrapolated from younger cohorts. The traditional threshold of FEV₁/forced vital capacity of <70% used in a younger population may be a normal finding in the elderly population.⁵⁴ For this reason, recent studies have suggested that the use of a Z score

may be more accurate.⁵⁵ Furthermore, reversible obstruction may be more difficult to establish in elderly people because these patients have an impaired response to β -agonists.⁵⁶ As with the younger population, a negative methacholine challenge can rule out asthma. On the other hand, a positive test is less useful because aging is associated with increased airway responsiveness.⁵⁷

Asthma is more commonly associated with dyspnea at rest but elderly patients have less perception of bronchospasm. This complicates the diagnosis and places them at higher risk for more severe disease.²⁵ One observation study comparing difficult-to-control asthma in adults and young cohorts showed that elderly people reported fewer symptoms and less use of medications despite worse lung function.⁵⁸ Thus, performing lung function tests in elderly patients could play a more critical role compared with the younger population. Because the cardiovascular responses to hypoxia and bronchoconstriction tend to diminish with increasing age, objective measures of asthma severity (peak flow monitoring and blood gas estimation) are essential in this age group.⁵⁹

The most common symptoms for asthma in the elderly population are the same as the younger population, *viz.*, wheezing, cough, and dyspnea. Nocturnal symptoms are associated with a mortality risk in one cohort study.⁶⁰ Exacerbations are most commonly triggered by a viral upper respiratory tract infection.^{2,61} This is particularly important given that age-related changes to the lungs and immune system increase the risk for lung infections and blunt the response to vaccinations such as influenza.¹⁴ Pneumonia and influenza are leading causes of death in the elderly population.²⁰ The lack of sensitive diagnostic tests and the prevalence of asymptomatic viral infections have made it difficult to establish causation. Other risk factors include obesity, tobacco use, allergen exposure, and genetic susceptibility.⁶² A meta-analysis showed both the incidence and the severity of asthma increases in obese patients.⁶³

Differential Diagnosis

A major reason for the misdiagnosis of asthma in elderly patients is caused by the broader differential diagnosis. It is estimated that >50% of patients who are >65 years old have at least three comorbidities.⁶⁴ Wheezing in elderly people can signal the exacerbation of other chronic diseases such as COPD, congestive heart failure, gastroesophageal reflux disease GERD, chronic aspiration, and malignancy.⁶⁵ Bronchial carcinoma and bronchiectasis can present with wheezing and cough.⁶⁶ It can be nearly impossible to distinguish asthma from COPD.^{67,68} Furthermore, a long history of asthma is an independent risk factor for COPD.⁶⁹

Methacholine airway reactivity and partial bronchodilator reversibility are common in COPD.² Age-related changes, such as neutrophilic inflammation, respiratory tract remodeling, and blunted response to bronchodilators further obscures the boundaries between these diseases. The clinical relevance of distinguishing between these diseases is important because medications such as leukotriene antagonists and omalizumab can be helpful for asthma but not COPD. A reduced FEV₁, regardless of the underlying cause, is a most important prognostic marker.⁷⁰

GERD commonly presents more like asthma in the elderly people.⁷¹ Furthermore, GERD, which commonly coexists with asthma, can exacerbate symptoms; thus, it should be well controlled.⁷² Congestive heart failure can present with wheezing and cough commonly in the morning.^{73,74} For congestive heart failure, the physical exam and chest x ray will likely show fluid overload. B-type natriuretic peptide levels and echocardiogram are also helpful. Bronchopulmonary carcinoma can cause lower airway obstruction and head and neck malignancies can cause upper airway obstruction. Medications such as aspirin, β -blockers, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs increase the risk of adult-onset asthma. Smoking-related lung diseases can increase the severity of asthma in adults.⁴¹

Management

The basic principles for managing asthma in the elderly population are the same as the younger population. The step-care pharmacologic protocol based on symptom severity and treatment response is the current standard.⁷⁵ Treatment guidelines may need to be adapted when applied to elderly patients. Problems more commonly encountered in managing asthma in the geriatric population include inability to distinguish asthma from other medical conditions, later presentation of disease, difficulties with inhaler technique, and poorer response to β -agonists.^{76,77} Underestimation of the severity of an acute exacerbation of asthma has been suggested as a contributory factor to poor outcome.⁵⁹ Older patients experience higher exacerbation frequency and required more hospitalizations and higher doses of steroids to get symptom control.⁷⁸ Remission rates are higher in younger patients.^{79,80}

β -Blockers are commonly used in this population. These drugs can trigger bronchoconstriction. Although the bronchodilator response to inhaled β -agonists declines with age, this is not the case for inhaled anticholinergics.^{81,82} Furthermore, an observational study that compared the response of elderly asthmatic patients to ipratropium and salbutamol showed a better response with ipratropium.⁸² Generally, inhaled anticholinergics have a good safety profile in elderly patients.^{83,84}

Corticosteroids reduce airway inflammation and enhance the action of β -agonists.⁸⁵ Elderly people are more sensitive to the side effects of systemic steroids such as osteoporosis and cataracts. Many patients already have underlying osteoporosis. The risk for bone fracture with the use of oral corticosteroids should be considered.⁸⁶ Although high-dose inhaled steroids are associated with decreased bone density, the evidence for fracture risk is conflicting. Recent meta-analysis found no association between the use of inhaled corticosteroids and fractures at low-to-medium doses. A slight increase in risk was seen in those using high doses.⁸⁷ Another recent meta-analysis looked at the long-term use of inhaled steroids in COPD patients and found a modest increased risk.⁸⁸ A dose-dependent risk was observed in a prospective cohort study.⁸⁹

Age-related changes in pulmonary function, immunity, and perception of symptoms has rendered the management of asthma in this population particularly challenging. Managing these patients is further complicated by the unique issues of this population, which include multiple comorbidities; declining functional status; and social issues such as housing, health insurance, and access to health care. These issues affect the ability for self-management and compliance. A multidisciplinary approach is needed. In addition to clinical assessments, which address issues such as multiple comorbidities and polypharmacy, this approach would include housing issues, functional status, nutrition, and cognitive and behavioral aspects. One cross-sectional study indicated that activity limitation, improper inhaler device usage, systemic inflammation, and noncompliance with a written action plan were among the most prevalent issues complicating the management of these patients.⁹⁰

The number of clinical management issues directly correlates with quality of life. The more complicated the management plan, the higher the risk of noncompliance. A team approach is important and should include primary care physicians, geriatric consultation where available, dietitians, physical therapy, social workers, and case managers. Pulmonary rehabilitation and nutrition are important aspects of geriatric care that are frequently overlooked. Management plans would include regular office visits, addressing health insurance, housing and financial issues, consideration for home health care, rehabilitation to improve ambulation, optimizing nutritional status, and more liberal use of nebulizers. Clinicians need to be educated about the risk and benefits of treating this population. In contrast to the younger population, goals of care centered on improved quality of life, rather than long-term outcome, may be more appropriate.

Psychological consultation may be considered to address depression and dementia, which are both highly prevalent in the geriatric population. These diseases

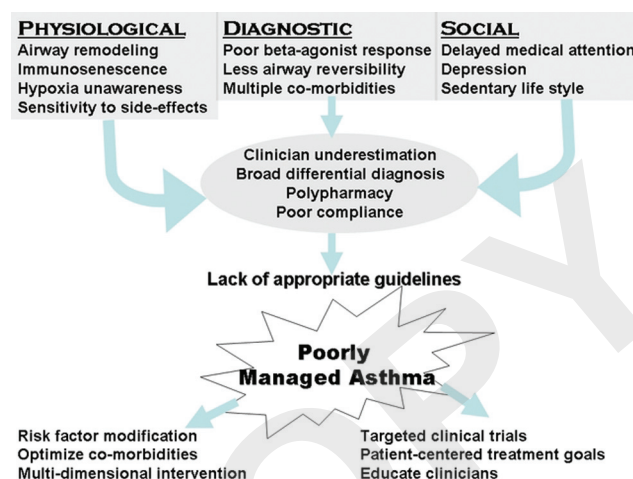


Figure 1. General algorithm summarizing the multiple issues leading to poorly managed asthma in the geriatric population. The goals of a multi-disciplinary approach are stated to help guide treatment.

are known to affect medical compliance and quality of life.⁹¹ Depression can influence a patients' perception of their health and severity of their symptoms. Depression has a negative impact on chronic illnesses such as dementia, heart disease, and diabetes.^{92,93} Screening for depression and cognitive decline is particularly important in the geriatric population because early intervention can significantly improve outcome. Encouraging patients to participate in their own health care is an important goal. These interventions can impact quality of life and lead to more effective management. Figure 1 summarizes the approach to asthma in the elderly population.

SUMMARY

Asthma is a highly prevalent disease in the geriatric population. It is a diagnosis that is frequently missed and associated with significant morbidity. Asthma contributes to poor general health status, depression, and limitation of activities of daily living.⁵ Compared with the younger population, asthma in the elderly population is associated with more frequent hospitalizations, more exacerbating triggers, a lack of symptoms despite severe disease, and a more progressive disease course that usually requires continuous treatment. Many issues unique to the geriatric population must be considered as well. Despite this, there is a lack of evidence-based guidelines in the elderly population. More effective management requires a multidimensional team approach with patient-centered goals of care. Specific management issues will likely be more easily identified and treated with this approach.

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