

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society Workshop Report: Evaluation and Management of Asthma in the Elderly

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Abstract

Asthma in the elderly (>65 yr old) is common and associated with higher morbidity and mortality than asthma in younger patients. The poor outcomes in this group are due, in part, to underdiagnosis and undertreatment. There are a variety of factors related to aging itself that affect the presentation of asthma in the elderly and influence diagnosis and management. Structural changes in the aging lung superimposed on structural changes due to asthma itself can worsen the disease and physiologic function. Changes in the aging immune system influence the cellular composition and function in asthmatic airways. These processes and differences from younger individuals with asthma are not well understood. Phenotypes of asthma in the elderly have not been clearly delineated, but it is

likely that age of onset and overlap with chronic obstructive pulmonary disease impact disease characteristics. Physiologic tests and biomarkers used to diagnose and follow asthma in the elderly are generally similar to testing in younger individuals; however, whether they should be modified in aging has not been established. Confounding influences, such as comorbidities (increasing the risk of polypharmacy), impaired cognition and motor skills, psychosocial effects of aging, and age-related adverse effects of medications, impact both diagnosis and treatment of asthma in the elderly. Future efforts to understand asthma in the elderly must include geriatric-specific methodology to diagnose, characterize, monitor, and treat their disease.

Keywords: aging; reactive airways disease; immunosenescence; lung function; phenotype

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Overview

There are now more Americans over the age of 65 years than at any other time in United States history, and their numbers increased 15.1% in the past decade (1). In 2014, 14% of the U.S. population was older than 65 years, and in other countries this number was considerably higher (2). The U.S. aging population is expected to increase rapidly over the next decade. Active asthma is common in patients older than 65 years of age and can be severe and disabling, with marked ventilatory impairment (3–5) and

negative impact on quality of life (QOL) (6). Asthma in older patients may persist from childhood or may begin in adulthood, even at an advanced age. Across the American lifespan, those who were 65 years and older had the largest increase in the prevalence of current asthma, from 6.0% in 2001 to 8.1% in 2010 (7). Importantly, this age group had the highest rate of asthma deaths and asthma-based physician office visits and the second highest rate of asthma hospitalizations (7, 8).

Asthma in the elderly (AIE) is underdiagnosed, misdiagnosed, and frequently undertreated (4, 9). There is limited information regarding many aspects (e.g., diagnosis, pathophysiology, and treatment) of asthma in this age group. Although there are many clinical and physiologic features of AIE that are similar to asthma in younger individuals, a number of confounding influences, such as comorbidities, impaired cognition and motor skills, and psychosocial effects of aging, complicate its management. A workshop by the National Institute on Aging (NIA) in September 2008 explored the pathophysiology, recognition, and care of AIE and identified a number of knowledge gaps (10). The American Thoracic Society (ATS) sponsored a workshop in May 2015 to discuss discoveries about AIE subsequent to the NIA proceedings to identify future directions to advance knowledge in the field.

Major conclusions from the workshop included the following:

1. Epidemiology of AIE

- Is common and increasing in prevalence (7, 11).
- Has high rates of morbidity and mortality; the most vulnerable older individuals with asthma are low-income African-American and Hispanic women.

2. Structural changes of the aging lung may worsen physiologic function in asthma

- With aging, there is loss of elastic recoil, increased airway remodeling in the smaller airways, and increased thickness of the central airway wall, which may act synergistically with asthma to worsen airflow obstruction.

3. Immune function and airway inflammation in older patients with asthma

- Aging itself is associated with altered immune response and increased systemic inflammation (“inflamm-aging”).
- Differences in airway inflammation between older and younger patients with asthma are not well characterized.
- Atopy is common in older patients with asthma; however, the role of antigen sensitization and exposure on disease severity is not defined.

4. Phenotypes of AIE

- Understanding of phenotypes of AIE is limited and must address age of asthma onset and overlap with chronic obstructive pulmonary disease (COPD), termed asthma-COPD overlap syndrome (ACOS).

5. Diagnosis of AIE

- There are no specific physiologic tests or biomarkers for the diagnosis and monitoring of AIE.
- Future AIE studies should include global geriatric assessment tools.

6. Treatment of AIE

- AIE treatment is complex due to potential reductions in cognitive and physical function, comorbidities, polypharmacy, and psychosocial challenges associated with aging.
- There is limited knowledge on optimal pharmacological management strategies and response to asthma medication in older adults, largely due to their exclusion from clinical trials.
- Adverse effects of asthma medications are more common in the elderly.

Introduction

Asthma was long considered a childhood disease. Little attention was given to asthma in elderly subjects until the Tucson epidemiologic study of obstructive lung disease (12–14). This longitudinal study reported that asthma is common, often severe, and associated with a high death rate in people older than 65 years of age. Subsequent work has demonstrated that asthma in the elderly (AIE) is generally poorly understood and, therefore,

underdiagnosed or misdiagnosed and undertreated (15, 16). An NIA workshop in September 2008 identified multiple gaps in understanding of the disease process of AIE and its management (10). One major question raised was whether the pathophysiology of AIE differs from asthma in younger patients. An ATS Workshop on The Evaluation and Management of Asthma in the Elderly in May 2015 addressed knowledge gained since the 2008 NIA conference. In this meeting, a group of clinicians and basic scientists with expertise on asthma and aging reviewed the current state-of-the-art knowledge and identified future directions for research. This article presents the summary of the workshop findings on AIE (i.e., defined as asthma in those older than age 65 yr).

Methods

Clinicians and researchers from various backgrounds (pulmonary medicine, allergy and immunology, geriatrics, and epidemiology) were selected for this workshop on the basis of their recognized interests and contributions in the field of AIE (Table 1). Key subtopics pertaining to AIE were selected by the Chair and assigned to workshop group members in alignment with their expertise. The Program Officer for Lung Biology from the NIA provided guidance for interfacing with the National Institutes of Health and for developing strategies for multidisciplinary research initiatives. Literature searches were performed with independence regarding search strategies, inclusion/exclusion criteria, and subtopic materials for discussion. Participants presented the current science in their field of expertise relevant to the aging lung and AIE. Discussion followed each presentation, and roundtable interactions helped achieve consensus on current understanding of AIE, limitations in knowledge, and future directions. The findings of the workshop were written by the participants and synthesized in the current report. Workshop participants who had industry relationships (e.g., industry-funded research) were recused from writing, editing, and commenting on related portions of the manuscript.

Results

Update on the Epidemiology of AIE

Asthma imposes a substantial health burden worldwide, affecting 300 million

Table 1. Methodology

| Methods Checklist | Yes | No |
|--|-----|----|
| Panel assembly | | |
| Included experts from relevant clinical and nonclinical fields | x | |
| Included individuals who represented patients and society at large | x | |
| Included methodologist with appropriate expertise (documented expertise in development of conducting systematic reviews to identify the evidence base and development of evidence-based recommendations) | | x |
| Literature review | | |
| Performed in collaboration with a librarian | | x |
| Searched multiple electronic databases | x | |
| Reviewed reference list of retrieved article | x | |
| Evidence synthesis | | |
| Applied preselected inclusion and exclusion criteria | | x |
| Evaluated included articles for sources bias | | x |
| Explicitly summarized benefits and harms | | x |
| Used PRISMA1 to report systematic review | | x |
| Used GRADE to describe quality of evidence | | x |
| Generation of recommendations | | |
| Used GRADE to rate the strength of recommendations | | x |

Definition of abbreviations: GRADE = Grades of Recommendation Assessment, Development, and Evaluation; PRISMA1 = Preferred Reporting Items for Systematic Reviews and Metaanalyses 1.

people and ranking 22nd in disability-adjusted life-years (17). In addition, 250,000 people worldwide die of asthma each year, due in part to limited access to treatment (17). Regions with high rates of asthma include those with increased urbanization and an aging population (17). Persons 65 years and older are especially vulnerable to adverse health outcomes including asthma-related events and reduced quality of life (QOL), given age-related reductions in cognitive and physical function, and increased rates of comorbid conditions (18–23). In addition, older Americans often live in urban environments (24), with higher traffic pollution predicting poorer asthma-related QOL (6).

The United States National Surveillance of Asthma report (7) shows that across the American lifespan, those aged 65 years or older had the: (1) largest increase in the prevalence of current asthma, (2) highest rate of asthma-related deaths, (3) second-highest rate of asthma-based physician office visits and hospitalizations, but unexpectedly (4) lowest rate of a reported asthma attack in the previous year or an emergency department (ED) visit for asthma. The most vulnerable older Americans were women, African Americans, Hispanics, and low-income groups. Although these observations may apply to other countries, similar

worldwide epidemiologic investigations are needed for confirmation (17).

Age-related factors may impact the epidemiology of AIE, including the discordant finding of lower rates of asthma attacks and asthma-based ED visits relative to higher rates of asthma deaths, hospitalizations, and physician office visits. Establishing an asthma diagnosis and determining asthma-related health care utilization may be confounded by several factors: (1) concurrent age-related increases in comorbidities (e.g., heart disease, chronic obstructive pulmonary disease [COPD], etc.), (2) multifactorial geriatric health conditions (i.e., cognitive and physical impairments), (3) adverse effects from polypharmacy, and (4) psychosocial factors (i.e., lower level of education, sedentary status, social isolation, and being homebound) (18–21, 25–27). Furthermore, evaluation of asthma-based symptoms may be limited by age-related reductions in awareness of symptoms (e.g., perception of wheezing) (28–30) and by the “paradox of well-being” (31). The latter phenomenon refers to high levels of life satisfaction in older persons, which can coexist with lower health expectations (31), thus increasing the likelihood that symptoms are missed or minimized in severity (i.e., delaying awareness of an asthma attack). This underrecognition of symptoms may lead to decreased utilization of ED services,

possibly leading to higher rates of hospitalization and death.

Update on the Effects of Aging on Lung Structure and Function as it Pertains to Asthma

To understand the interaction of asthma and aging on lung structure and function, it is critical to first review the effects of aging in the normal lung. It is implicit that there is biologic heterogeneity of the aging lung, characterized by great interindividual variability in chronologic physiologic change (10). With normal aging, the collagen fiber network that coils around the alveolar ducts changes, producing alveolar duct dilation and homogenous enlargement of alveolar air spaces (32–36). The alveolar air space enlargement that occurs in the “senile” lung differs from emphysema, because there is no associated inflammation or alveolar wall destruction (34). Alveolar enlargement decreases alveolar surface tension and, in turn, decreases elastic recoil pressure. Degenerative changes of the spine contribute to kyphosis and, in combination with increased convexity of the sternum, increase the anteroposterior diameter of the chest (33, 36). Concurrently, chest wall compliance decreases due to the spinal changes and to stiffening of the rib cage and reduced thickness of the parietal muscles (33–35, 37, 38). Respiratory muscle strength deteriorates due to decreased curvature of the diaphragm, sarcopenia (i.e., loss of muscle mass and function), and inadequate nutrition (32–34, 36–39).

Age-related alterations in lung structure impact physiologic function (32–39). The reduction in static elastic recoil pressure decreases expiratory flow (i.e., FEV₁). In healthy nonsmokers, there is an ~30-ml decline in FEV₁ yearly starting after age 30 years (32, 35, 38), with an accelerated decline in both FEV₁ and FVC between age 65 and 93 years (40). The FEV₁/FVC ratio also declines with aging (34), producing a more “obstructive” flow volume loop (39). Residual volume (RV) increases by about 50% between ages 20 and 70 years as a result of early airway closure secondary to reduced lung recoil combined with reduction in chest wall compliance and respiratory muscle strength (34, 35, 38, 39). By age 65 years, closing volume approaches FRC, so that airways close even during tidal breathing (34, 39).

This results in ventilation–perfusion mismatch and widening of the alveolar–arterial gradient. FRC also increases with aging, whereas total lung capacity remains relatively unchanged, because the increased RV is counterbalanced by the decreased vital capacity. Diaphragmatic strength in a 76-year-old is about 25% lower than in a 20- to 30-year-old (35), and inspiratory and expiratory respiratory muscle strength steadily declines between ages 65 to older than 85 years in both sexes (39). The decreased airway caliber in the elderly that results from these mechanical factors may enhance the consequences of smooth muscle shortening after inhalation of a bronchoconstrictor stimulus, contributing to increased airway hyperresponsiveness (AHR) (41) with aging.

In elderly patients with asthma, pathologic changes of asthma may synergize with those of normal aging to affect lung structure and function (Figure 1). Loss of elastic recoil is reported in chronic asthma in varying age groups (42, 43). This may contribute to airflow reduction independent of airway remodeling, a characteristic feature of asthma in patients of all ages. Studies of small and large airway wall area and thickness in older versus younger individuals with asthma have shown conflicting results by computed tomography (CT) scans and autopsy assessments (44, 45). It is likely that aging alone does not lead to airway remodeling; however, longer duration of asthma may lead to increased airway narrowing due to progressive remodeling and increase in

airway smooth muscle volume (45). Thus, factors attributable to asthma alone, combined with those due to normal aging, may account for the accelerated decline in FEV₁ in asthma noted longitudinally in some large population studies (46, 47). The impact of age of asthma onset and of disease duration on airway function in the elderly requires further study.

Update on the Effects of Aging on Immune Function and Airway Inflammation

With advanced age, there are alterations in both innate and adaptive immune responses termed “immunosenescence” (Table 2). In addition, aging is associated with low-grade, chronic, systemic inflammation, referred to as “inflamm-aging,” characterized by increased IL-1β, IL-6, and tumor necrosis factor-α (48). Effects of immunosenescence and inflamm-aging on airway inflammation and its regulation in older individuals with asthma are not well established. However, there are some studies that have provided some insight.

Eosinophils from aged subjects may have some decreased effector functions, but data on their role in AHR are conflicting. The development of AHR later in life was associated with elevated peripheral blood eosinophil counts in men (mean age, 60 yr) enrolled in the Normative Aging Study (49). However, peripheral eosinophils from subjects with asthma (55–80 yr) exhibited decreased degranulation in response to IL-5 stimulation and a trend for decreased superoxide production when compared

with cells from patients 20 to 40 years of age (50), whereas there was no difference in eosinophil leukotriene C4 production (51). In a mouse model of asthma, although antigen-sensitized and airway-challenged aged mice developed greater bronchoalveolar fluid eosinophilia than younger mice, AHR was lower in the former, suggesting that increased airway eosinophilia was not correlated with AHR (52). Taken together, these studies suggest that although age-associated changes in eosinophils exist, the clinical implications of these changes and their relationship to asthma phenotypes in older patients remain unclear.

The number of airway neutrophils increases in older individuals without airway disease (53–55), and peripheral neutrophils have increased primary granule release and neutrophil elastase activity, which could lead to increased tissue damage (56). Older compared with younger patients with asthma have increased sputum neutrophils, but the impact of inflamm-aging on this increase has not been addressed (44, 50, 57, 58). Airway neutrophilia in older patients with asthma corresponds to increased levels of sputum neutrophil mediators, including matrix metalloproteinase-9, neutrophil elastase, and IL-8 (58), as well as increased systemic inflammation (e.g., C-reactive protein and IL-6) (59). This resembles changes seen in a severe asthma phenotype noted in some younger adults (60). Aged mouse models of asthma have demonstrated increased expression of airway IL-8 and cytokines associated with Th17 cells (61, 62). This could contribute to increased airway neutrophilia. Determining the type of underlying airway inflammation in older adults with asthma is important, as neutrophilic asthma is often less responsive to corticosteroid treatment (63, 64).

The role of regulatory T cells (Tregs) in younger patients with asthma, though not clearly established, most likely suppresses airway inflammation and AHR (65–67). Peripheral Treg cell numbers are lower in younger patients with asthma than in age-matched healthy subjects (68). Another study reported that older patients with asthma had decreased peripheral Treg cells compared with age-matched normal control subjects (69), but the importance of Treg cells in AIE has not been widely investigated. We are unaware of any studies that directly compare Tregs in older versus

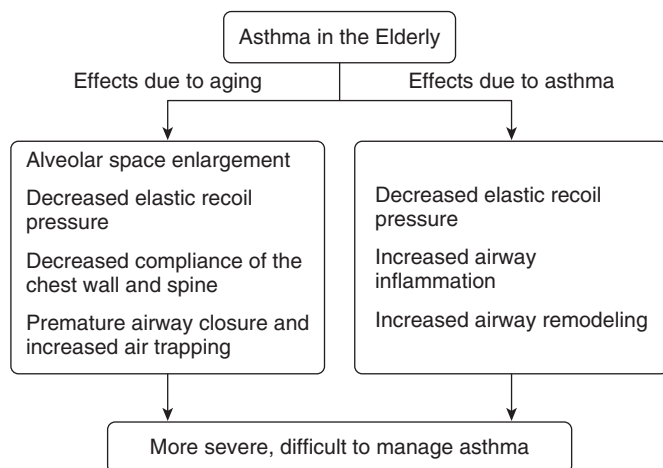


Figure 1. In the elderly patient with asthma, pathologic changes of asthma may synergize with those of normal aging to affect both lung structure and function. This may potentially lead to more severe and difficult-to-control disease.

Table 2. Features of immunosenescence: potential impact on asthma in the elderly

| Type of Immunity | Cell Type | Observations |
|----------------------------|------------------|--|
| Innate | Eosinophil | <ul style="list-style-type: none"> ↑ Peripheral eosinophilia and AHR in men (Normative Aging Study) ↓ Degranulation of peripheral eosinophils in older patients with asthma |
| | Neutrophil | <ul style="list-style-type: none"> ↑ BALF neutrophils and neutrophil elastase activity with aging in patients without asthma ↑ Sputum neutrophils in older versus younger patients with asthma ↑ Levels of sputum neutrophil mediators in older patients with asthma (e.g., IL-8, MMP-9, neutrophil elastase) |
| Adaptive cellular immunity | Tregs | ↓ Peripheral Tregs in older patients with asthma versus aged control subjects |
| | T cells | ↑ Proinflammatory cytokines with aging (inflamm-aging) |
| Adaptive humoral immunity | Humoral immunity | ↓ Antibody response to vaccines |

Definition of abbreviations: AHR = airway hyperresponsiveness; BALF = bronchoalveolar lavage fluid; MMP = matrix metalloproteinase; Tregs = regulatory T cells.

younger patients with asthma. However, aged mice fed low-dose antigen before sensitization (to induce oral tolerance and increase Treg expression) and challenge developed suppressed features of asthma, including decreased bronchoalveolar fluid total cell count and eosinophils, cytokine production, and AHR, suggesting that Tregs maintained function with aging (70).

Telomere shortening is believed to be associated with normal aging (71). During replicative senescence, telomere shortening may signal cell cycle arrest or apoptosis (72, 73) or release proinflammatory proteins (74). Shortening of telomere length in peripheral blood mononuclear cells correlated with increased asthma severity in a small group of patients with asthma (aged 25–60 yr) (75). We are not aware of any study that specifically examined telomere shortening in AIE.

Current Understanding of Phenotypes of AIE

Phenotypes, the outward manifestation of an individual’s underlying genetics, have been widely accepted as a way to characterize patients with asthma (76–81) and include clinical, physiologic, inflammatory, and molecular features. Stratification of asthma subtypes by phenotype and endotype (i.e., specific biologic mechanisms) represents the cutting edge for advancing asthma treatment. Despite the significant health

burden of AIE, we are aware of only one study exclusively characterizing this population. Park and colleagues (82) evaluated 872 patients older than 65 years of age using cluster analysis to segregate them into groups with common features and to assess the risk of asthma exacerbation in each cluster. A key finding from the study was that the cluster with the longest duration of asthma was more at risk for acute exacerbation than clusters with more recent asthma onset and more normal lung function. Long duration of asthma and smoking (two distinct clusters) were associated with accelerated lung function decline. Although other investigators, including those from the Severe Asthma Research Program (76), have used a similar analytic approach and have identified patients with “late-onset asthma” (LOA), very few of the individuals included exceeded age 65 years. In one study (83), patients with “longstanding asthma” (LSA) reportedly had more atopy than those with “late-onset disease,” but the latter category was not limited to elderly subjects. Others have found that staphylococcal enterotoxin might be a risk factor for LOA that may, in some cases, be nonatopic (32, 84). One “simplistic” approach to phenotyping elderly asthma would be to separately evaluate those with LSA, LOA, and ACOS (85). This may be challenging because of lack of uniform definitions of LSA and LOA as well as

uncertainty about the exact definition, prevalence, and overall significance of ACOS (86). Distinguishing patients with ACOS is important, because they experience more frequent exacerbations and poorer QOL (86). AIE displays many of the hallmarks of COPD (87), and patients with LOA are often misdiagnosed with COPD or other diseases, such as congestive heart failure (85). There are no biomarkers that definitively distinguish elderly from younger patients with asthma, although sputum cellularity is generally more neutrophilic in AIE. Thus, current methodologies to phenotype AIE are insufficient. In addition, several cohort studies have demonstrated that over long follow up, it is not uncommon for patients to change from one cluster designation to another (88–91). Investigations dedicated to phenotypic and endotypic characterization of AIE are therefore needed to facilitate diagnosis and treatment.

Physiologic Tests and Biomarkers in the Diagnosis and Management of Elderly Patients with Asthma

Many of the same tests used in younger patients with asthma are useful to characterize AIE (Table 3). Spirometry and airway reactivity measurements are first-line methods for diagnosing and monitoring AIE, as in younger patients, although the nature of the airway disease may differ in the elderly. Many studies show lower FEV₁ and more severe airflow limitation in older patients with asthma (44, 92, 93). Bronchoprovocation testing can detect airway reactivity in older as in younger patients (44, 94), and older patients tend to have more peripheral airway closure during bronchoconstriction (measured by the reduction in FVC) than younger patients with asthma (92). When evaluating spirometry in older patients, age-adjusted values are essential, particularly when interpreting the FEV₁/FVC ratio, to avoid overdiagnosing respiratory impairment (95). Although predicted values for spirometry are available for the elderly (96), data for nonwhite individuals and for those older than 75 years are sparse. An important limitation of spirometry, and thus also of standard bronchoprovocation tests in the elderly, is that these involve effort-dependent maneuvers. Although studies (97, 98) have shown that 80% or more of older persons can achieve ATS-acceptable spirometry, this may be hard for some frail

Table 3. Diagnostic and treatment comparison of elderly and younger patients with asthma

| Test/Characteristic | Elderly | Young |
|--------------------------------------|---|--|
| Spirometry | May be less useful in frail patients; reference standards not widely available | Generally useful tool to assess asthma severity |
| Bronchodilator responsiveness eNO | May be less pronounced May be useful | Variable but generally greater May be useful |
| Methacholine challenge | Less often used because of more frequent contraindications (e.g., cardiovascular disease) | Useful; overall fewer contraindications |
| Atopy | Less common | Common |
| Comorbidities | COPD, heart disease more common | Allergic rhinitis more common |
| Phenotypes | Limited knowledge, but late-onset asthma, long-standing asthma, and ACOS described | Multiple phenotypes described |
| Sputum cellularity | Generally more neutrophilic | Generally more eosinophilic |
| Therapy | No age-specific guidelines Optimal regimen unknown More susceptible to adverse effects due to comorbidities, drug-to-drug interactions, and polypharmacy Inability to use certain inhalers due to lack of dexterity and reduced inspiratory flow | Guideline-specific regimens in place that address the needs of most patients |

Definition of abbreviations: ACOS = asthma-COPD overlap syndrome; COPD = chronic obstructive pulmonary disease; eNO = exhaled nitric oxide.

elderly patients (99–101). The FEV₁/FEV₆ may be a more easily obtained surrogate for FEV₁/FVC in such individuals (102, 103). Bronchoprovocation challenges may be contraindicated in some elderly patients due to low baseline lung function and cardiac comorbidities.

Forced oscillation may be useful to follow older patients with asthma, as it provides an effort-independent evaluation of respiratory system mechanics. Forced oscillation measures changes in lung impedance, and data obtained at different frequencies of applied pressure provide insight into abnormalities in different lung regions. Inoue and colleagues found that elderly patients with asthma had significantly greater resistance of the respiratory system at 5 Hz, significantly greater frequency dependence of resistance (resistance at 5–20 Hz), and more negative reactance at 5 Hz than younger patients with asthma (44). These observations suggest an abnormality particularly in the lung periphery, perhaps reflective of increased heterogeneity or enhanced airway closure during quiet breathing in elderly patients with asthma.

Imaging may have utility in evaluating AIE. Chest CT is a noninvasive modality used to assess lung structure, and measurements at different lung volumes can

be used to make inferences about lung function. Chest CT in elderly patients with asthma shows increased wall thickness and increased air trapping compared with younger patients with asthma (44). Xenon ventilation CT in the elderly shows that dyspnea severity correlates with xenon gas-measured air trapping, and decreases in gas trapping correlate with improvements in FEV₁. However, these techniques are limited by the complexity of the measurements and the need for specialized imaging and analysis algorithms not readily available in clinical practice. The expense and risks of radiation exposure also obviate CT use.

Exhaled nitric oxide (eNO) is a biomarker in younger patients with asthma. Bozek and colleagues found slightly higher eNO levels in very elderly patients with asthma (≥80 yr) than in a younger cohort of patients with asthma (18–30 yr) (104). Other studies report similar levels in older and younger patients with asthma (44). Porsbjerg and colleagues found that eNO levels correlated with airway reactivity in the elderly (105); this has been demonstrated in younger individuals as well (106, 107). Overall, these studies suggest that eNO likely has similar diagnostic and monitoring capabilities in both older and younger patients with asthma.

Update on Strategies to Manage the Elderly Patient with Asthma

Current evidence-based guidelines for asthma (86, 108) are derived from studies on younger individuals, as older patients are frequently excluded from clinical trials (109). Only a few reports have addressed the management of the elderly population with asthma (10, 110). It is widely accepted that asthma is often undertreated in older patients (111–113), likely due to multiple factors (Table 3), including incomplete understanding of pathophysiology and most appropriate age-related therapy, decreased asthma self-management with aging, misdiagnosis of AIE, poor access to health care, comorbidities, medication costs, fear of corticosteroid use, and poor medication delivery technique (114–117). The appropriate management of any chronic disease in the elderly, including asthma, should include multidimensional assessment (MDA) of physical, psychological, cognitive, and social factors that may impact successful treatment.

Nonpharmacological management strategies. Optimal asthma management for all patients incorporates avoidance of known asthma triggers. Elderly patients may have allergy-triggered asthma, although the role of allergen sensitization in the

Table 4. Progress of understanding of asthma in the elderly: limitations and future directions

| Topic | Limitation | Advances Since NIA Workshop | ATS Workshop Recommendations for Future Directions |
|---|---|---|--|
| Epidemiology | Absence of age-specific asthma guidelines for older patients resulting in under- and misdiagnosis Distinguishing health care utilization records to identify care of asthma vs. other comorbid conditions | Not accomplished | Develop geriatric-specific guidelines and geriatric-specific survey instruments for the diagnosis of asthma. Develop a more precise definition of AIE. Develop a survey instrument to better capture health care utilization for AIE. |
| Effect of aging and asthma on lung structure and function | Incomplete understanding of structural and functional changes in aging plus asthma vs. aging or asthma alone | Studies using HRCT scans of the lung and forced oscillation testing | Define normal structural and functional age-related changes in the lung (from the cellular to whole-organ level). Establish interval imaging of cohorts of aging individuals to better understand structural changes in the lung. |
| Effect of aging and AIE on immune function | Confounding effects of changes in immune function and inflammation with aging (i.e., inflamm-aging). Lack of understanding of potential differences in airway inflammation between older and younger patients with asthma Unclear role of allergen sensitization and exposure in older patients with asthma | Additional data on neutrophilic inflammation in AIE | Investigate systemic and lung-specific inflammatory changes in normal aging and in aging plus asthma. Define the roles of allergen sensitization and exposure in onset, progression, and exacerbation of AIE. |
| Appropriate models for studying AIE | Difficulty obtaining lung tissue and BALF from older patients Translation of aged animal studies to human studies. | Some new animal model data on neutrophilic inflammation in AIE | Develop novel allergic and nonallergic models of asthma, reflecting altered immune cell and cytokine milieu of the aging lung. Establish biobanks of lung tissue, sputum, blood, and other samples from older subjects with and without asthma. |
| Asthma phenotypes | Lack of uniform definitions and incomplete characterization of longstanding versus late-onset AIE Incomplete understanding of the ACOS | Generally not accomplished. Staphylococcal enterotoxin has been identified as a potential risk factor for late-onset asthma. Although ACOS is not completely understood, the term was first proposed after the NIA workshop. | Design studies in older patients with asthma of different ages of onset, incorporating clinical/historical (e.g., tobacco use), physiology, imaging, indices of airway inflammation, molecular biomarkers, and response to treatment in order to characterize phenotypes and endotypes in this population. Reach consensus definition on late-onset asthma. |
| Physiologic tests and biomarkers in AIE | Confounding effects of aging on physiologic testing on AIE (i.e., comorbidities, decreased respiratory muscle strength, cognitive impairment) | Useful reference standards for individuals up to age 95 yr were published in 2012, after the NIA workshop. However, data for nonwhite individuals and for individuals >75 yr of age are still lacking. | Establish age-appropriate reference standards for better interpretation of lung function in the elderly, particularly for nonwhite individuals and those of extreme age. Develop more age-appropriate (i.e., effort independent) physiologic tests to assess AIE. Investigate the role of currently available biomarkers in older patients and identify novel biomarkers to increase insight into AIE. |

(Continued)

Table 4. (Continued)

| Topic | Limitation | Advances Since NIA Workshop | ATS Workshop Recommendations for Future Directions |
|--|--|---|--|
| Management strategies for AIE | Complexity of management of AIE due to comorbidities, polypharmacy, medication adverse effects, and psychosocial factors Lack of inclusion of older patients in clinical trials for new asthma therapies Potential age-related altered response to existing asthma therapies (e.g., ICS) | Not accomplished despite increased awareness of the complexity of AIE | Develop specific guidelines for managing AIE, incorporating a multidisciplinary approach. Enroll elderly patients in clinical trials to better understand age-specific treatment response and safety factors. Explore novel routes of medication delivery (e.g., inhaled delivery devices not dependent on technique or inspiratory flow, transdermal, etc.) |
| Incorporation of geriatric care into asthma care | Common geriatric health issues (e.g., impaired cognition, reduced strength including reduced lung function, and frailty) may limit use of certain therapies. | Not accomplished, although emphasized more specifically in the current report than in the NIA proceedings | Develop studies incorporating comorbidities in asthma treatment to assess the effect of multifactorial geriatric health conditions on the clinical trajectory of asthma in older persons. Explore role of pulmonary rehabilitation in AIE, as patients commonly suffer from physical dysfunction. |

Definition of abbreviations: ACOS = asthma-COPD overlap syndrome; AIE = asthma in the elderly; ATS = American Thoracic Society; BALF = bronchoalveolar lavage fluid; HRCT = high-resolution computed tomography; ICS = inhaled corticosteroids; NIA = National Institute on Aging.

population is less well defined than in younger patients. Detecting and managing comorbidities that may exacerbate asthma are essential to optimize asthma control. Although influenza vaccination is recommended for all patients with asthma (118), it is underutilized in the elderly patient with asthma (119). Furthermore, the immune response to the vaccine may wane with aging, especially in patients on high-dose inhaled corticosteroids (120–122). The long-term benefit of pulmonary rehabilitation in elderly asthma, although described in few published reports, is unknown (123–126).

Asthma education is important in managing asthma but may be more difficult in older populations due to physical and cognitive function decline. Unfortunately, asthma education in elderly patients is poorly implemented (127). An MDA to asthma care in older patients has been shown to identify additional significant clinical issues compared with a diagnosis-centered approach (128). The MDA should include: (1) standardized evaluation of comorbidities and screening for frailty and psychosocial impediments to care using geriatric-specific tools, (2) assessment of barriers

to adherence to inhaled therapy, (3) individualization of treatment incorporating age- and disease-specific factors, and (4) multiple points of care and assessment including social workers, pharmacists, nurses, certified asthma educators, and physicians.

Pharmacological management strategies. Current pharmacological management of AIE is based on guidelines developed for younger patients with asthma with Th2-high or eosinophilic airway inflammation. Studies have shown that Th2 immune deviation may not be generalizable to all patients with asthma, particularly the elderly (58, 63, 129). Limited inclusion of older patients in clinical trials and alterations in medication pharmacodynamics and pharmacokinetics associated with aging impedes conclusions on optimal asthma management in this population. Traditional lung function measurements to evaluate asthma medications in clinical trials may be less useful in the elderly due to increased prevalence of irreversible obstruction. Outcomes that are symptom-driven may be more effective (130, 131). Furthermore, careful monitoring of inhaler technique (due to decreased muscle strength and loss of coordination), medication adherence,

and potential adverse reactions to asthma medications are essential (130, 132–134).

Rescue medications. Although β_2 -receptor responsiveness and affinity may decline with age, this has not been consistently established (135, 136). However, elderly patients may be more sensitive to adverse effects of β_2 -agonists, particularly those with unstable cardiovascular disorders (137, 138). Animal models suggest that parasympathetic activity decreases with aging due to reduced receptor numbers or postreceptor coupling, but relatively little is known about the effect of aging on anticholinergic responses in humans. Short-acting anticholinergic medications may be useful bronchodilators in the elderly and do not have the cardiac side effects of β_2 -agonists. Although more likely with oral agents, cognitive impairment, falls, symptomatic urinary outlet obstruction, and closed-angle glaucoma are potential risks of inhaled anticholinergics and should be used with caution (139).

Controller therapies. Inhaled corticosteroids (ICS) constitute the cornerstone of chronic asthma management, yet they are underutilized in elderly patients (112, 140, 141). ICS use reduces hospital admissions and mortality in this population (142). However, corticosteroids may be less effective in older

patients with asthma with predominantly neutrophilic inflammation; this needs further study. Older patients receiving higher-dose ICS should be monitored closely for potential decreased bone mineral density, increased fracture risk, and cataracts (143, 144). The safety of long-acting β -agonist use in older patients, particular those with underlying cardiovascular disease, has been most studied in COPD, and results are inconsistent. Some studies suggest that when used, especially as monotherapy, there is increased risk of cardiovascular events (145, 146), whereas other studies have not shown this (147, 148). Studies specifically focused on the safety of this class of drugs in elderly patients with asthma are lacking; however, the black box warning for use of long-acting β -agonist as monotherapy applies to all patients with asthma. Long-acting muscarinic antagonists have been shown to be efficacious as add-on therapy in patients with asthma up to age 75 years old (149) and may be especially helpful in patients with concomitant COPD (ACOS).

A few studies have reported that leukotriene modifying agents may benefit AIE (131, 150). Although significant improvement in asthma indices was observed in older age groups, it was less pronounced than in younger patients with asthma (131) and in older patients treated with ICS (150). Some older patients with asthma have demonstrated clinical improvement after treatment with anti-IgE therapy (151, 152). Specific immunotherapy has also been effective in older patients and should be considered, but risks and benefits must be weighed carefully (153, 154).

Comorbidities That Influence Disease Severity, Diagnosis, and Management of AIE

Comorbidities in asthma worsen disease severity and QOL in all individuals (155), but more likely to a greater degree in older patients (156, 157). Concomitant medical conditions are more common in older patients (158). Some comorbidities of older patients with asthma that typically differ from those of younger patients include atrial fibrillation (159), congestive heart failure (157), and COPD (15). Distinguishing AIE from COPD (15) in older adults is difficult, and some older patients may have components of both diseases, or ACOS (160). The prevalence of bronchiectasis

increases with aging (161), and coexistence with asthma is associated with more severe asthma (162), more hospitalizations, and increased risk of chronic respiratory failure (163). As in younger patients with asthma, chronic rhinosinusitis in people older than 65 years is strongly associated with the diagnosis of asthma (84, 164, 165), in particular when associated with IgE sensitization to staphylococcal enterotoxin (84). Obesity, often prevalent in the elderly, is associated with poor asthma control and asthma exacerbations (166). Gastroesophageal reflux disease increases with age (167), likely due to age-associated reductions in lower esophageal sphincter pressure, and this may contribute to asthma exacerbations (168). Cognitive impairment and change of mood (depression and/or anxiety) are also common in geriatric patients, decrease QOL (169), and negatively influence adherence to asthma treatment (169, 170). Most importantly, they have been shown to be independent correlates of mortality in AIE (137). Sleep disorders are more prevalent in elderly patients with asthma than in age-matched control subjects (171) and in young patients with asthma (172) and have been associated with low QOL (171, 172).

Comorbidities may interact with asthma therapy by modifying the pharmacokinetics and pharmacodynamics of asthma medications. Renal or hepatic diseases, for example, can impair the absorption, distribution, metabolism, and excretion of drugs, thus increasing risk of side effects (173). Even patients with normal serum creatinine can have reduced glomerular filtration rates, so that the risk of side effects related to renal dysfunction should not be underestimated (174). Furthermore, some medications used to treat comorbidities may worsen asthma (e.g., β -blockers, aspirin, nonsteroidal antiinflammatory drugs, cholinergic agents, etc.). Comorbidities are also invariably associated with polypharmacotherapy, an important risk factor for adverse drug reactions in the elderly. Aging, *per se*, is also responsible for pharmacokinetic changes (175), which should be accounted for when developing a pharmacotherapy plan.

Limitations and Future Directions

Advances in knowledge about AIE have been hindered by multiple factors (Table 4). Diagnosing and phenotyping AIE is

confounded by the effects of normal age-related changes in the lung, by underreporting of symptoms, and by comorbidities. In addition, absence of a precise definition for AIE, lack of appropriate models to study the disease, and failure to include older adults in clinical trials contribute to gaps in understanding. Although there has been some progress since the NIA proceedings, major research questions remain unanswered. Recommendations for future directions were established by consensus of the current workshop group.

Conclusions

In May 2015, the ATS sponsored a workshop to evaluate and report on discoveries about AIE since the NIA workshop and to identify future directions to advance knowledge in this field. AIE, a complex entity with poorly understood phenotypic heterogeneity (including inflammatory profiles), is impacted by comorbidities of advancing age, such as heart disease, concomitant lung disease (e.g., COPD), cognitive impairment, and depression, and also by natural changes of the aging respiratory and immune systems. Although asthma in persons aged 65 years and older has had the largest increase in prevalence and the highest mortality of any age group, geriatric-specific guidelines are not available for diagnosis and treatment of AIE. Physiologic tests for elderly patients with asthma are the same as those used in younger individuals, and age-appropriate inflammatory biomarkers have not been identified. As the population is aging, AIE will present a greater future management issue. Therefore, it is imperative that research efforts focus on characterization of AIE to enhance diagnostic and treatment strategies for this vulnerable population. ■

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