Introduction

The US population over the age of 65 years is projected to grow from about 40 million in 2005 to over 86 million by 2050 [1]. In 2004, the US prevalence of asthma for those 65 years or older was 7%, with 1,088,000 reporting an asthma attack in the previous 12 months [2]. Older asthmatic patients are more likely to be underdiagnosed, undertreated [3,4] and hospitalized than younger asthmatic patients aged 4–64 years [2]. They also have the highest death rate (51.3 per million people) of any age group [2]. Older women are hospitalized more than twice as often as older men [2].

Recent interest in asthma in the elderly

There have been two large workshops in the United States that explored asthma in the elderly (AIE). The first was sponsored by the National Heart, Lung, and Blood Institute in 1996 [5]. In October 2008, the US National Institute of Aging sponsored another workshop on AIE. The proceedings of that workshop are not yet published but many of the participants’ publications will be cited here. The European Respiratory Society recently published a monograph [6**] on respiratory diseases in the elderly, which includes a comprehensive review of AIE.

Biology of aging

In order to understand AIE, it is helpful to review some aspects of the biology of aging. Aging is a natural process and not a disease. Many of the anatomic and physiologic changes seen in asthma have also been described in the aging lung, suggesting that the aging process may be a contributing factor to the deterioration of lung function with progressive age [7,8,9**]. ‘Senile emphysema’ characterized by airspace dilatation resulting from loss of supporting tissue without alveolar wall destruction has also been described in elderly individuals. In fact, aging is an important determinant of decreased lung density on computed tomography scan in asthmatic patients [10]. Furthermore, aging is thought to be a proinflammatory condition associated with a dysregulated immune system, and aging-associated immune remodeling in the elderly is thought to play a significant role in the pathogenesis of many chronic inflammatory diseases such as Alzheimer’s dementia and other neurologic diseases, cardiovascular disease, type 2 diabetes mellitus, arthritic diseases,
Anemia, osteoporosis and cancers. Evidence suggests that immunity deteriorates with age [11,12], but immunosenescence is not an unavoidable and progressive decline of all immune functions, but rather a product of continuous remodeling of various parts of the immune system over time [13]. Both branches of the immune system are clearly affected by aging, adaptive more so than innate immunity. Aging results in changes in immune cell function that have been described for T cells, macrophages, neutrophils, dendritic cells and eosinophils [14]. Age-related changes in peripheral blood eosinophil effector functions have been recently described, a fact that may affect manifestations and response to therapy of certain allergic diseases such as asthma in the elderly population [14]. Frailty is a distinct syndrome associated with functional decline, loss of independence and mortality. Frailty occurs in 7% of those 65 years old and 40% of 80 year olds in the United States and is associated with increased risk of comorbidities, impacts on physical and cognitive function, reduced functional reserve, susceptibility to stress and diseases and predicts negative health outcomes including nursing home placement [15]. Features of frailty include osteopenia, sarcopenia, low-grade anemia, inflammatory profile, functional impairment, cognitive impairment and vulnerability, and can occur without any specific disease. Frailty may also be associated with systemic inflammation and correlates with markers of systemic inflammation, including C-reactive protein and high interleukin (IL)-6 levels [16].

**Phenotypes of asthma in the elderly**

Many asthma phenotypes have been described [17]. Rackemann [18] first described extrinsic and intrinsic asthma in 1947. New interest in intrinsic asthma has recently risen, and several speculations about its mechanisms and pathogenesis have been described including the role of a persistent microbial link [19,20]. As such, AIE may also have specific phenotypes. It appears that age of onset, and thus duration of AIE may be important in delineating at least two such phenotypes: late-onset asthma (LOA) and long-standing asthma (LSA). LOA (with onset in childhood or in early adulthood) and LSA (onset after middle age) may indeed have different clinical presentation, disease course and response to treatment, similar to what one encounters with type 1 and type 2 diabetes. In reviewing the literature, LSA and LOA share some features, but may have different causes and very different prognosis (Table 1) [21]. In the future, personalizing the diagnosis and treatment of AIE based on these different phenotypes may lead to improved outcomes.

### Pathogenesis and risk factors of asthma in the elderly

Airway inflammation plays a major role in asthma including AIE. The National Asthma Education and Prevention Program Report 3 [22] addresses the pathophysiology of inflammation in asthma in general, but does not address LOA or asthma in the older adult. The Global Initiative for Asthma (GINA) [23] describes inflammation as an essential feature of asthma, but states that its pathogenesis and cause are not clear. Most patients with asthma present with eosinophilic inflammation, although neutrophilic inflammation is seen in some patients, especially those with severe disease. Neutrophilic inflammation is notoriously resistant to corticosteroid therapy, and thus its presence may have therapeutic implications.

In a model of sensitized mice, airway inflammation and mucus metaplasia after antigen challenge was more pronounced in older mice than younger mice, but at the same time the increase in airway hyperresponsiveness was much less pronounced [24]. This suggests an aging-related attenuation of airway response to inflammation. Furthermore, the inflammatory cytokine response to antigen was different in older as compared with younger sensitized and challenged mice [24]. These findings need to be replicated in humans as they may reflect different phenotypes with potentially different response to treatment.

The roles of different inflammatory pathways and mediators of inflammation described in asthma have not been well studied in the elderly with asthma [25,26]. Proteases found in dust mites, molds and other biological pollutants may trigger Toll-like receptors to

### Table 1 Potential mechanisms for the asthma phenotypes in the elderly

<table>
<thead>
<tr>
<th>Age of onset (years)</th>
<th>Genetic role</th>
<th>Infection</th>
<th>Allergy</th>
<th>Inflammation</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSA Child or young adult (&lt;40)</td>
<td>Likely gene by environment</td>
<td>Viral – rhinovirus and RSV</td>
<td>Likely</td>
<td>Th2 driven, eosinophilic</td>
<td>Allergens, daycare, school and workplace</td>
</tr>
<tr>
<td>LOA Adult (&gt;40)</td>
<td>Likely epigenetic, including oxidative stress and shortened telomeres</td>
<td>Viral – RSV, influenza and bacterial (e.g. Chlamydia pneumoniae), microbial superantigens</td>
<td>Likely</td>
<td>Unlikely Th1 or Th2 driven, neutrophilic and/or eosinophilic, innate immunity, Th17, proteases</td>
<td>Workplace, dwelling type (house, apartment and institutional)</td>
</tr>
</tbody>
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LOA, late-onset asthma; LSA, long-standing asthma; RSV, respiratory syncytial virus; Th, T helper cell.
The development of neoplastic diseases in this population to persistence in airway inflammation, this may facilitate to start the apoptosis process [27]. In addition to leading patients with asthma present with reduced susceptibility mechanism to remove senescent cells. However, older generally increased in the elderly, perhaps as a defensive aging and airway inflammation seen in asthma has not been extensively studied, but there may be an additive effect of one to the other.

Resistance of different inflammatory cells to initiate apoptosis in asthmatic patients, causing persistence of airway inflammation, has been described. Apoptosis is generally increased in the elderly, perhaps as a defensive mechanism to remove senescent cells. However, older patients with asthma present with reduced susceptibility to start the apoptosis process [27]. In addition to leading to persistence in airway inflammation, this may facilitate the development of neoplastic diseases in this population [7*].

The role of genes, and especially epigenetic changes associated with multiple replications associated with aging, and with oxidative stress and other environmental effects on genes are not yet fully understood. The genetics of asthma are not well defined, with many candidate genes but no single gene or gene family standing out. It has been proposed that this is because asthma is not a single disease in the sense of a well defined entity with established cause, but rather a syndrome with several related inflammatory conditions, with a common clinical presentation [28–30,31*,32**].

Respiratory infections, especially viral [rhinovirus and respiratory syncytial virus (RSV)], are common precipitants of initial wheezing and asthma exacerbations in infants and young children. Viral and bacterial infections have also been implicated as the precipitating cause of the initial onset of asthma and exacerbations in adults, but only few studies linking infection to AIE have been published. Evidence of infection with low levels of these organisms may persist intracellularly in clinically well older people. Persistence of such respiratory infections may play a central role in the development of LOA. However, it is very difficult to culture or identify these organisms while at subclinical levels [19*,33,34,35**]. Furthermore, there is evidence that microbial superantigens such as staphylococcal enterotoxins can amplify airway inflammation and thus may have an important role in the pathogenesis and progression of asthma [20*].

Atopy is commonly associated with both the initial onset of allergy and exacerbations of asthma in children and younger adults. Allergies are commonly associated with LSA, but much less likely to be associated with LOA. In reviewing studies of allergen sensitization of asthmatic patients not separated by age of onset, the presence of a positive allergy test ranges from zero to 75% [36]. However, atopy rate determined by skin prick test tends to decrease with aging [37]. In fact, when allergen sensitization is compared by age of onset, there is a marked difference with early-onset asthma (LSA) positive skin tests or specific immunoglobulin E (IgE) tests ranging from 56 to 62% and LOA ranging from zero to 24%. These studies are rather small and a meta-analysis would not be appropriate, but they clearly suggest that older age of onset is associated with less allergy sensitization (Table 2) [21,38,39]. In addition, allergy tests in older patients do not seem to correlate well with nasal provocation studies or the presence of allergens in the home environment [40**,41–43].

Obesity may be associated with increased inflammation and may cause mechanical impairment of diaphragm excursion. Obesity and metabolic syndrome tend to be clustered in the elderly population.

Female sex is associated with increased prevalence, increased hospitalization and higher death rates in AIE. In the asthma surveillance study of 2004 [2], women at the age of 20 years have nearly double the prevalence of asthma as men, by menopause this increases to triple and continues into old age. The mechanism for this sex difference in the prevalence of AIE is not well understood. One potential explanation may be related to hormonal differences; estrogen or estrogen receptors in the respiratory system may enhance airway inflammation or bronchial hypersensitivity in women or testosterone may be protective in men [44].
Older adults may live in older homes [45] with increased exposure to molds, insects and rodents. It remains unclear whether moving to an institutional setting such as an assisted living facility or nursing home alters the course of asthma in the elderly patients. One could speculate that a more ‘sterile’ environment might help an asthmatic patient who is allergic, but crowding could also lead to more infections leading to more exacerbations.

Diagnostic challenges of asthma in the elderly
Symptoms of AIE may mislead physicians to consider causes other than asthma such as ‘old age’, chronic obstructive pulmonary disease (COPD) and heart failure [4,8,9**]. Atopic diseases are often not considered in older patients and AIE is often confused with COPD, a common misdiagnosis that is related to old age and disability [3]. Furthermore, the use of important tools such as spirometry, which are essential to diagnose airway obstruction in this population, continues to be underutilized in the primary care setting. Even when these tests are utilized, confusion exists as to what physiologic parameters define asthma in the aging population [9**] and often the patient’s condition, physical or cognitive function, may prohibit the performance of effective testing. Aging significantly influences bronchodilator responsiveness in patients with asthma [46]. The diagnostic value of postbronchodilator pulmonary function testing in differentiating asthma from COPD is of questionable value in the older population [47].

Similarly, older people with asthma tend to attribute their breathlessness to their aging process and often do not perceive that they are slowing down or decreasing their activities because of their disease. Alterations in the perception of airflow obstruction due to aging often lead to underestimation of the disease severity and thus the delay in seeking advice [48].

Several systemic comorbidities may coexist with AIE. This may be related to the inflammatory pathways common to these comorbidities and asthma. However, this issue needs further evaluation. Such comorbidities, which include atherosclerosis, diabetes, metabolic syndrome, and respiratory infections such as pneumonia and influenza [7*], need to be carefully addressed in great detail. Furthermore, the presence of such comorbidities or their treatments may complicate the course of asthma and the response to its treatment.

Management challenges of asthma in the elderly
Even in those with a diagnosis of asthma, physicians may concentrate on treating other comorbidities such as cardiovascular disease, diabetes and other common problems in the elderly, overlooking the appropriate treatment of asthma [4,49,50]. In addition, many older patients frequently do not want to or cannot afford to take ‘prophylactic’ or preventive medicines for a disease they do not perceive as a chronic problem.

The presence of psychomotor and cognitive disabilities in this population may also affect the choice of inhaler delivery systems that can be used to deliver asthma medications [8,51]. The use of nebulization therapy may be ideal in such situations [51].

Treatment of AIE may be complicated by the potential for drug interactions and increased incidence of adverse effects [8]. However, the lack of many drug trials involving elderly patients with asthma limits our ability to make conclusive remarks about the efficacy, safety and tolerability of currently available asthma medications. Furthermore, the presence of multiple comorbidities in this population possibly arising from the increased systemic inflammation emphasizes the need for future medications that target common pathophysiologic mechanism(s).

Conclusion
We have many unanswered questions about the pathogenesis and risk factors for AIE. Epigenetic changes, infections (especially viruses, but maybe some bacteria), allergic and nonallergic inflammation, obesity, sex, perhaps the inflammation seen in normal aging and possibly other environmental exposures may play a role in causing asthma in this population. Further studies are needed to fully explore the differences between the two distinct phenotypes in AIE in regards to their clinical presentations, course of disease and response to therapy. The diagnosis and treatment of AIE are difficult in the presence of multiple comorbidities. In addition to addressing such comorbidities in these patients, the goals of management should include achieving and maintaining asthma control, improving health status and prevention of emergency room visits and hospitalizations.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

- **of special interest
- ***of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 78).

This is an excellent review of the current state of the art in understanding AIE from a European point of view.

Braman SS, Hanania NA. Asthma in older adults. J Am Geriatr Soc 2009; 57:901–909. This is a recent comprehensive review of the topic of AIE.


Ferrucci L, Corsi A, Lauretani F, et al. The GINA is an excellent source to review what is known about asthma in all age groups and what little is known about AIE.

Busse PJ, Kilaru K. Complexities of diagnosis and treatment of allergic respiratory diseases. J Allergy Clin Immunol 2006; 117:94–102. This study demonstrates that positive skin test or specific IgE does not predict positive nasal challenge to dust mite allergen in older adults, suggesting skin or serum antibodies do not predict nasal response to dust mite allergen. There are no similar bronchoprovocation studies in older adults.

Simola M, Holopainen E, Malmberg H. Changes in skin and nasal sensitivity similar bronchoprovocation studies in older adults. Ann Allergy Asthma Immunol 2008; 101:12–17. This study demonstrates that positive skin test or specific IgE does not predict positive nasal challenge to Dermatophagoides pteronyssinus in older adults. Ann Allergy Asthma Immunol 2008; 101:12–17. This study demonstrates that positive skin test or specific IgE does not predict positive nasal challenge to Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005; 352:1749–1759. This study demonstrates that positive skin test or specific IgE does not predict positive nasal challenge to asthma or COPD via IL-13 produced by macrophages that have been stimulated by natural killer T cells. This can occur after the virus has been cleared to very low levels.


Simola M, Holopainen E, Malmberg H. Changes in skin and nasal sensitivity similar bronchoprovocation studies in older adults. Ann Allergy Asthma Immunol 2008; 101:12–17. This study demonstrates that positive skin test or specific IgE does not predict positive nasal challenge to respiratory viral infection into chronic lung disease such as asthma or COPD via IL-13 produced by macrophages that have been stimulated by natural killer T cells. This can occur after the virus has been cleared to very low levels.


