



Asthma in the elderly

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Asthma is a common disease with an overall prevalence in the general population of 6% to 7% [1]. A higher prevalence of disease is found in the elderly; it is estimated that 7% to 9% of individuals over the age of 70 has asthma. Asthma in the elderly can have a profound impact on quality of life and cause medical utilization to be high. New onset asthma can occur at any age, even in the eighth and ninth decades of life. Despite the frequent occurrence of asthma in the elderly, it is a diagnosis that has been frequently overlooked and even when discovered it is often undertreated [2–8]. There are a number of important reasons why there is underdiagnosis and undertreatment of asthma in the elderly. These reasons are discussed in this review. This review also focuses on the epidemiologic, clinical, and pharmacological aspects of asthma in the geriatric population. A proper evaluation of asthma symptoms can lead to early diagnosis, proper treatment, and avoidance of unnecessary emergency department visits and hospitalizations.

The definition of asthma

An expert panel of the National Institutes of Health (NIH) has provided us with the most widely accepted current definition of asthma [9]. The first report of this group, published in 1991 and often referred to as the “NIH Asthma Guidelines,” was updated as the “Expert Panel Report 2” in 1997. The following is the most universally accepted definition of asthma.

Asthma is a chronic inflammatory disease of the airways in which many cells play a role, in particular, mast cells, eosinophils, and T-lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partially reversible either spontaneously or with treatment.

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This inflammation also causes an associated increase in airway hyperresponsiveness to a variety of stimuli.

Pathophysiology

Asthma is caused by a complex interaction of cells, mediators, and cytokines that result in inflammation [9–11]. The characteristic cellular changes involve (1) constitutive cells such as epithelial cells, mucous glands, endothelial cells, and myofibroblasts; (2) resident cells such as bone-marrow derived mast cells and macrophages; and (3) infiltrating cells such as eosinophils, CD4 (helper cell) T-lymphocytes, neutrophils, basophils, and platelets. These inflammatory cells are capable of generating a wide variety of mediators that can induce bronchoconstriction. A number of typical histopathologic findings can be found in the airways of asthmatics.

Histopathologic findings

Infiltration of the airways by inflammatory cells such as mast cells, eosinophils, activated T-lymphocytes, and neutrophils can be demonstrated by bronchial biopsies and inferred by demonstrating increased numbers of these cells on bronchoalveolar lavage. The number of activated lymphocytes found in bronchial biopsies has been correlated with the number of local activated eosinophils and the severity of asthma.

Specific cytokines, most of which are products of lymphocytes and macrophages, appear to direct the movement of cells to the site of airway inflammation. They also activate the cells, causing them to release their mediators.

Mast cells, usually as a result of IgE-mediated stimulation, also release preformed mediators such as histamine and proteases and further act as a regulator of inflammation by producing cytokines that promote eosinophil infiltration and activation. Several mast cell products induce bronchoconstriction and cause increased mucus secretion.

Denudation of the airway epithelium can lead to airway edema and loss of substances in the mucosa that protect the airway. Epithelial damage promotes bronchial hyperresponsiveness because access by irritating substances to sensory nerve endings is increased.

One of the characteristic findings in severe asthma is the presence of tenacious mucus plugs in the airways. Death from asthma usually occurs from blockage of the airways by diffuse mucus plugging.

Edema of the airway mucosa is due to increased capillary permeability with leakage of serum proteins into the interstitium. A number of cell-derived mediators are capable of inducing edema formation, including histamine, prostaglandin E, LTC₄, LTD₄, LTE₄, platelet-activating factor, and bradykinin.

Thickening of the reticular basement membrane, the lamina reticularis, is observed with light microscopy and is a constant feature of asthma. There is also

evidence of increased bronchial smooth muscle mass that contributes considerably to the thickness of the airway wall. The airway architecture is also changed by the deposition of type III and V collagen and fibronectin beneath the basement membrane. This has been referred to as “subepithelial fibrosis.” The architectural changes seen in and beneath the basement membrane and in the bronchial smooth muscle are referred to as airway remodeling and are thought to cause permanent changes that result in fixed airflow obstruction.

Physiologic mechanisms

Neurogenic influences

There is growing evidence that the neural control of the airways is abnormal in asthma and that neurogenic mechanisms might augment or modulate the inflammatory response [10]. The autonomic nervous system regulates many aspects of airway function such as airway tone, airway secretions, blood flow, microvascular permeability, and the release of inflammatory cells. It is likely that autonomic dysfunction is caused by inflammation because inflammatory mediators can modulate the release of neurotransmitters from airway nerves.

Bronchial hyperresponsiveness

Airway inflammation is thought to be a key factor in producing a cardinal feature of asthma—bronchial hyperresponsiveness (BHR) [10]. Bronchial hyperresponsiveness can be described as an exaggerated bronchoconstrictive response by the airways to a variety of stimuli such as aeroallergens, histamine, methacholine, cold air, and environmental irritants. It is not clear whether or not bronchial hyperresponsiveness is acquired or genetically determined to appear with the appropriate stimulus. It is thought that airway inflammation is the stimulus for bronchial hyperresponsiveness as it can be induced by a number of inciting events including viral respiratory infections, allergic reactions, and noxious agents such as ozone and sulfur dioxide. The degree of bronchial hyperresponsiveness can be determined in the pulmonary function laboratory by standard inhalation challenge testing. The methacholine inhalation challenge is the most frequently used clinical tools to determine the presence and degree of bronchial hyperresponsiveness. Bronchoprovocation testing is a safe, effective method to uncover asthma in the elderly [1,12].

Airway responsiveness and aging

There is evidence that some sympathetic and parasympathetic nervous system functions are diminished with age [13,14]. This decline in autonomic nervous system function is consistent with a generalized diminution of peripheral somatic nerve function that occurs with aging. While the protective laryngeal gag reflex appears diminished in normal elderly subjects [15], there is evidence that the

cholinergically mediated cough reflex is not similarly affected [16]. This is also true of cholinergic bronchoconstrictive reflexes because most studies have shown that bronchial reactivity to methacholine does not change with age [17]. There is a relationship between the degree of bronchial hyperresponsiveness and prechallenge pulmonary function; a low FEV₁ predicts heightened responsiveness [18]. This might explain why some studies have shown that bronchial responsiveness is heightened in the elderly.

Reduced β -adrenoreceptor responsiveness has been demonstrated in normal elderly men and women. When compared with young and elderly normal subjects, elderly late-onset asthmatics have been shown to have reductions in β -adrenergic receptor affinity while maintaining normal receptor density. There is also evidence that post-receptor events are impaired in the aged because cyclic AMP production by pathways that are independent of adrenergic receptor stimulation is depressed [19]. The bronchodilator response to inhaled β -agonists declines with age [20–22]. This is not the case with anticholinergic agents.

Airway obstruction

Airway obstruction is another cardinal feature of asthma. The causes of airflow limitation in asthma are (1) acute bronchoconstriction, (2) mucus plugging of airways, (3) bronchial wall edema, (4) inflammatory cell infiltration, (5) airway wall remodeling (fibrosis), (6) smooth muscle hypertrophy, and (7) uncoupling of elastic recoil forces.

Inflammation of the bronchial wall can uncouple the mechanical linkage between the lung parenchyma and the airways, thereby reducing the normal lung recoil forces that keep the airways open. This might contribute to airway narrowing and also to BHR. During an acute attack of asthma airway resistance increases and pulmonary function tests of airflow are abnormal.

Atopic asthma

Allergic or atopic reactions in the upper (nose, sinuses) and lower airways are both important in the pathogenesis of asthma in childhood and young adulthood. Their role in the elderly is less clear. The term extrinsic asthma has been used to describe patients whose asthma is triggered by exposure to inhaled aeroallergens. Atopy is defined by the presence of abnormal amounts of IgE antibodies in response to contact with environmental antigens and can be manifested as asthma, eczema, or seasonal and perennial allergic rhinitis. This can be demonstrated clinically by the presence of elevated total or specific serum IgE levels in the blood or by demonstrating positive skin prick tests to a variety of standardized aeroallergens.

Atopy and aging

Atopy is an age-related phenomenon; in community surveys the peak prevalence of immediate skin test reactivity occurs during the third decade of

life and falls rapidly after age 50 [23]. The proportion of asthmatics that are atopic varies with age; 80% in childhood, 50% between ages 20 and 40, and less than 20% after age 50. Serum IgE levels are often elevated in elderly asthmatics, and high levels are closely related to the likelihood of a subsequent asthma diagnosis in younger adults [24]. The reported prevalence of allergic asthma after age 65 has varied considerably. In one study of elderly asthmatics followed in a pulmonary clinic [25], patients who had acquired their asthma at an early age had a greater likelihood of previous allergic disease such as eczema or seasonal allergic rhinitis. None of the patients who had acquired asthma after age 60 had a previous atopic history. Immediate hypersensitivity skin tests to 43 aeroallergens in this group were uniformly negative and IgE levels elevated in about 20% of patients. This compares with a 36% positive skin test rate in elderly asthmatics identified from a community-based survey [26].

Other recent studies [7,27–29] have explored the relationship between allergy and asthma in the elderly. One was conducted on patients over age 65 with moderate and severe persistent asthma recruited from the medical, geriatric, and allergy clinics of a tertiary health center [28]. Allergy skin tests were positive to at least one allergen in 75% of patients. Five of the seven most prevalent reactions were to indoor allergens such as cat and dog dander and cockroach dust mites. Bermuda grass was the second most prevalent positive skin test. Home visits were performed to sample for indoor allergens. Although the majority of homes had high levels of indoor allergens, there was no correlation between home allergens above significant levels and severity of asthma measured by lung function testing and no evidence presented that exposure to these aeroallergens caused worsening of asthma symptoms. Another study [7] was reported with data collected from the Cardiovascular Health Study, a clinical study conducted by randomly sampling elderly individuals from four US communities. This study showed that many elderly asthmatics report that their respiratory problems started in childhood. While skin testing and IgE levels were not available in the study patients, about half of the patients reported that wheezing was triggered by contact with plants, animals, or pollens and was seasonal.

A history of atopy is the strongest predictor of asthma in the elderly [30]. Patients who are capable of becoming sensitized will have done so by the time they are older adults. There is a complex interplay between allergens and asthma; some allergens causing sensitization, some enhancing the allergic response, and some actually inducing asthma attacks. Although atopy might be important in the pathogenesis of asthma of some elderly asthmatics, in general it is rare to find clinical provocation of asthma by common aeroallergens, a dominant feature in this age group. Nonetheless, avoidance of potential allergens in the environment of the elderly asthmatic should be advised.

Non-atopic asthma

The term intrinsic asthma is used to describe patients who have none of the typical features of atopy, including a positive family history of allergy and

asthma, positive immediate hypersensitivity reactions to skin prick-tests, and an elevated serum IgE level. As noted, such patients are in general older than atopic asthmatics and have a later onset of asthma. Bronchial biopsy studies performed on patients who have intrinsic asthma have been compared to a group of patients with extrinsic asthma with a comparable severity of symptoms [11]. There is a more intense inflammatory cell infiltrate in the bronchial mucosa of the intrinsic asthmatics with leukocytes, macrophages, and CD3 and CD4 cells. Patients who have intrinsic asthma have an exaggerated T-cell response to maintain the same degree of symptoms and BHR. This might mean that intrinsic asthma involves activation by an (as yet) unidentified antigen. Putative non-allergic antigens that might cause such reactions include viral antigens or inappropriately recognized “self antigens.” In support of the former causative agent, it noteworthy that the majority of elderly patients who develop asthma after age 65 have their first asthmatic symptom preceded immediately by or concomitant with an upper respiratory tract infection [3].

Epidemiology

It has been difficult to assign precise figures to the prevalence and incidence of asthma in the general population because studies do not often clearly distinguish asthma from other obstructive lung diseases. Both men and women who develop typical asthma after age 40 usually have prior symptoms of cough and sputum production and often have pulmonary function abnormalities prior to the diagnosis of asthma [31]. Thus, in many older patients it is not possible to distinguish asthma from chronic bronchitis, especially in current or former cigarette smokers. A label of “asthmatic bronchitis” seems more appropriate for such patients. Community surveys in which a physician diagnosis of asthma was required have provided data on asthma in the elderly [31–33]. The prevalence of active asthma in these studies, which represented new cases minus those in remission, peaked in early childhood at about 8% to 10% of the population, declined to approximately 5.5% during late adolescence, then rose again to about 7% to 9% during late adulthood (age > 70 years). In 1987, data from the National Center for Health Statistics showed that in the 65 to 74 age group, the rate for active asthma or wheeze was 10.4% compared with 9.6% in the 45 to 64 age group, 6.9% in the 18 to 44 age group, and 5.7% in younger teenagers [34].

In another report from a population-based cohort of elderly individuals living in Rochester, Minnesota, a group of asthmatics were identified with the onset of asthma after age 65 [3]. The age-specific incidence of asthma in patients aged 65 to 74 years of age was 103/100,000, 81/100,000 in patients aged 75 to 84 years, and 58/100,000 in patients older than 85 years.

Even more alarming are the statistics regarding morbidity and mortality in the elderly. In England and Wales in 1985, 58% of the men and 71% of the women whose deaths were attributed to asthma were older than 70 [35]. In the

United States, a study of asthma deaths of patients who had died in hospitals or nursing homes revealed that 80% of the deaths occurred in patients aged 55 and older [36]. Seventy-five percent of these patients were known to be smokers or ex-smokers. A careful analysis of these cases revealed that many younger asthmatics did clearly have asthma and had died of a severe sudden attack. In patients over age 55, confounding factors were much more prevalent. These patients frequently had underlying chronic bronchitis or COPD, were admitted to the hospital for nonrespiratory problems, and died of chronic respiratory failure. Less aggressive therapy was given to these elderly patients, both in the outpatient setting and during hospitalization. Often there was a delay in seeking medical care, and this was thought to be a major factor in their deaths. In the authors' view, only 10 of 33 patients over age 55 had pure asthma as a likely cause of death. The study suggests that current statistics might overestimate the true mortality from asthma in this age group. The study also suggests that many elderly patients with asthma-like symptoms and a history of previous smoking have COPD as an underlying or even dominant feature of their disease.

Clinical characteristics

Data on the clinical features of asthma in the elderly have been derived from both longitudinal community surveys and case studies [3,7,25,26,37,38]. Studies have consistently shown that symptoms caused by asthma are frequently overlooked by elderly patients and their physicians. Underdiagnosis and misdiagnosis of asthma are frequent in this age group. The most common symptoms reported are cough, wheezing, and dyspnea, similar to younger asthmatics. Exertional dyspnea and paroxysmal nocturnal dyspnea are present in a smaller number of patients. Unlike younger adults with asthma, a family or personal history of atopy is usually absent. Blood and sputum eosinophilia are common, but not universal. Because large community studies have shown that most patients first develop asthma in childhood or adolescence, many physicians have the misconception that asthma is a childhood disease. Other studies [25,26] have suggested that up to 40% of individuals are at least 40 years old at the time of their first attack of asthma. Another reason why asthma has been an overlooked diagnosis is that asthma symptoms are common in other diseases of the elderly. The hallmark symptoms of asthma, including shortness of breath, wheezing, and cough, are mimicked by and often confused with such diseases as congestive heart failure, emphysema, chronic bronchitis, COPD, chronic aspiration, gastroesophageal reflux, and tracheobronchial tumors [39]. It has been known for more than a century that early morning wheezing is a prominent symptom of congestive heart failure, which can also cause the clinical picture of asthma [40]. Elderly asthmatics do not, however, have a higher prevalence of cardiovascular disease than non-asthmatic patients [41]. Typical symptoms of gastroesophageal reflux in the elderly, such as vomiting and heartburn, might be absent. In a study [42] of elderly patients who had esophageal

reflux proven by intraesophageal pH monitoring, chronic cough, hoarseness, and wheezing were present in 57% of patients. In addition to causing asthma-like symptoms, there is also evidence that gastroesophageal reflux might be a cause of worsening asthma.

Objective measures of lung function such as spirometry and peak flow measurements are generally underutilized in elderly patients, and this also contributes to the delay or absence of diagnosis [3]. Lung function testing is especially important in this age group because there is an age-related reduction in the perception of dyspnea seen in the elderly [43]. Many elderly patients are fearful of having an illness and dying and are reluctant to admit they are having symptoms. Even when they do so, they might underestimate them or consider them the results of normal aging. Underreporting of symptoms in the elderly can have many causes including depression, cognitive impairment, social isolation, denial, and confusing symptoms with those of other comorbid illnesses.

The rate of smoking among elderly asthmatics (10% to 13%) is about half that of the general adult population. Lung function is generally lower in those who smoke compared with those who do not smoke due to concomitant COPD [26]. Even in those who do not smoke, the majority of elderly asthmatics have moderate to severe asthma. For instance, Burrows et al [26] reported on 46 patients with asthma who were 65 years or older at the time of enrollment in a longitudinal study of a general population sample. Many of these elderly asthmatics had severe disease with marked ventilatory impairment. Almost half admitted to frequent wheezing attacks or wheezing on most days, whereas only 30% of the group had rare attacks of shortness of breath with wheeze. The number of unscheduled ambulatory visits, emergency visits, and hospitalizations are high in elderly asthmatics, confirming the high degree of morbidity in this age group. Quality of life scores are generally low in patients with persistent asthma when compared with elderly patients with mild asthma or no asthma at all. Patients frequently report poor health, depression, and a significant limitation of activities of daily living [7].

Fixed airflow obstruction in elderly asthmatics

There is growing evidence that the airway function of young and middle-aged asthmatics declines at a greater rate than normal subjects [44–47]. The rate of decline increases with increasing age and in those who smoke cigarettes. In late-onset asthma, lung function declines rapidly shortly after diagnosis but then remains fairly stable. These effects on asthmatics are variable because not all individuals show a steeper rate of decline. The precise reasons for this individual variability have not been defined, although there is evidence that atopy and marked bronchial hyperresponsiveness [47] are two important risk factors. The long duration and severity of previous disease are also important factors [48,49], although many elderly asthmatics with severe airflow obstruction might be symptomatic for a relatively short duration of months to a few years. In one random survey of 1200 elderly asthmatics over age 65 from the

Mayo Clinic, only one in five patients had normal pulmonary function ($FEV_1 > 80\%$ predicted) while a similar number showed moderate to severe airflow obstruction ($FEV_1 < 50\%$ predicted) after administration of an inhaled short-acting bronchodilator [50]. The cause of chronic persistent airflow obstruction in asthma has not been explained. Structural changes of emphysema are minimal and airway remodeling is thought to be the main cause [51].

Treatment

General principles

Population studies of asthma in the elderly have shown that unlike many younger adults who often require no medications or just as-needed β -agonist therapy for occasional symptoms, most older asthmatics need continuous treatment programs to control their disease. At a time when memory loss is common and financial resources are often limited, many older patients require complicated and frequent dosing with multiple expensive drugs. Unfortunately, this has led to a significant rate of noncompliance among the elderly. Attempts to identify patients at high risk for noncompliance have failed. Gender, socio-economic factors, educational level, marital status, and severity of disease do not seem to be good predictors of compliance [52]. It is common in geriatric patients to live alone, and this places additional barriers to appropriate care. Such patients often suffer from inadequate nutrition and lack of immediate physical and emotional comfort. Often compassionate and sympathetic support from the physician and the office staff can be as beneficial as pharmacologic intervention. Sensitivity to economic issues can lead to prescriptions that cost less. Written lists of medications and dosing schedules are especially helpful and frank, open discussions about such issues as loneliness, finance, and loss of autonomy from chronic illness are appreciated. Furthermore, because of the patient's advanced age itself, the illness might pose an exaggerated threat of dying. This might lead to denial and undermedication or high anxiety and over-reliance on medication, physician visits, and office phone calls.

There are both short-term and long-term therapeutic objectives for every asthmatic patient [9]. Short-term objectives are the control of immediate symptoms and response to decreasing peak flow rate measurements. Long-term objectives are those directed to disease prevention because there are now well-proven strategies to avoid serious exacerbations of acute bronchospasm, which often lead to emergency room visits or hospitalization. To meet these therapeutic objectives, four components of asthma care should be addressed.

- 1) Optimal treatment of asthma depends on a careful assessment of the patient's symptoms and objective monitoring by office spirometry and home peak expiratory flow rate (PEFR) measurements. Older patients with asthma have been shown to deteriorate for longer periods prior to

hospital admission for severe acute asthma than younger patients. In a study of hospital admissions for asthma comparing patients over age 65 with those under age 40, 65% of elderly patients had worsening symptoms for more than 14 days before admission compared with 29% for the younger group [53]. One reason for this delay might be the blunted perception of breathlessness that has been found in the elderly compared to younger patients [43]. Monitoring of lung function with peak flow meters or office spirometry is therefore essential in caring for many elderly asthmatics.

- 2) Treatment of asthma with bronchodilator and anti-inflammatory medication is tailored to the patient's needs and relies on a staging system that is based on symptoms and objective measures of lung function.
- 3) Measures should be taken to avoid respiratory irritants that can cause worsening of symptoms. As with asthma at any age, education concerning avoidance of aggravating factors that can lead to severe bronchospasm is useful. Aeroallergens are less important in provoking symptoms in the elderly than in young subjects. The most important provocative factors include viral respiratory infections, irritants such as cigarette smoke, paints, varnish, household aerosols, etc, and pharmacologic agents that are often prescribed for concomitant illnesses. β -adrenoreceptor antagonists (β blockers) commonly used for ischemic heart disease, arrhythmias, and hypertension might precipitate bronchoconstriction in any asthmatic [54]. This includes both non-cardioselective agents (propranolol, pindolol, and timolol) and, to a lesser extent, cardioselective agents (metoprolol and acebutolol) [55–57]. Topical β -blockers are also widely used in the elderly to reduce intraocular pressure in wide-angle glaucoma. With such treatment, sufficient systemic absorption might occur, causing fatal status asthmaticus [58]. The severity of β blocker-induced bronchoconstriction correlates with the severity of underlying airflow obstruction and the degree of bronchial reactivity, and it might be reduced by the use of a cardioselective topical β -blocking agent such as betaxolol [59].
- 4) Patient education can be a powerful tool in asthma control. Family members also can be helpful, especially with elderly adults. Active participation by a patient in monitoring lung function, avoidance of provocative agents, and decisions regarding medications provide asthma management skills that give patients the confidence to control their own disease.

Treatment protocols for asthma

A global strategy for asthma management and prevention has been offered in the NIH Guidelines [9]. Treatment protocols use step-care pharmacologic therapy based on the intensity of asthma symptoms and the clinical response to these interventions. As symptoms and lung function worsen, step-up or add-on therapy is given. As symptoms improve therapy can be “stepped down.” The

Table 1
Asthma treatment by severity of disease

Mild intermittent asthma
Severity
Symptoms less than 2 \times /wk; nocturnal symptoms less than 2 \times /mo; FEV ₁ and PEFR > 80% predicted; PEFR variability < 20%
Treatment
Inhaled short-acting β 2-agonist prn
Mild persistent asthma
Severity
Symptoms > 2 \times /wk and < 1 \times /d; nighttime symptom > 2 \times /mo; FEV ₁ and PEFR > 80% predicted; PEFR variability 20–30%
Treatment
Begin anti-inflammatory therapy; inhaled corticosteroids preferred or consider a leukotriene pathway modifier or cromolyn. Short-acting β -agonist prn for quick relief, but increased use means need for additional controller therapy
Moderate persistent asthma
Severity
Daily symptoms and daily use of rescue β 2-agonist; >2 exacerbations/wk and 1 nighttime exacerbation/mo; FEV ₁ and PEFR 60–80% predicted; PEFR variability >30%
Treatment
Add long-acting β -agonist; if symptoms still persist can increase dose of inhaled corticosteroid, add leukotriene pathway modifier, or consider theophylline; continue short-acting β 2-agonist for acute relief
Severe persistent asthma
Severity
Continuous symptoms; limited physical activity; frequent exacerbations; frequent nighttime symptoms; FEV ₁ and PEFR < 60% predicted; PEFR variability >30%
Treatment
Inhaled corticosteroids; long-acting β -agonist; theophylline; and oral corticosteroid

Abbreviations: FEV, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

severity classification and recommended treatment protocols are presented in Table 1.

Medication for asthma

Anti-inflammatory agents

Anti-inflammatory agents are capable of reducing airway inflammation, improving lung function, decreasing bronchial hyperreactivity, reducing symptoms, and improving the overall quality of life. Corticosteroids are the most useful anti-inflammatory agents. Corticosteroids act by preventing migration and activation of inflammatory cells, interfering with the production of prostaglandins and leukotrienes, reducing microvascular leakage, and enhancing the action of β -adrenergic receptors on airway smooth muscle. They are available for oral, parenteral, and inhaled use. Oral preparations such as prednisone are useful for acute exacerbations of asthma unresponsive to

bronchodilator therapy. Doses of 40 to 60 mg/day are given until the patient responds, then the dosage can be slowly tapered. Poorly controlled asthma often requires daily or every-other-day maintenance with prednisone in dosages of 10 to 15 mg. Intravenous corticosteroids, usually given as methylprednisolone 60 to 80 mg every 6 to 8 hours for 1 or 2 days, are effective within 4 to 6 hours of administration in preventing further progression of the severe asthma exacerbation that requires hospitalization.

Inhaled corticosteroids are safe and effective treatments for persistent asthma whether it is mild, moderate, or severe. Inhaled corticosteroids have been in use for more than 20 years with excellent results [60]. Metered dose inhalers (MDIs) or dry powder formulations are available as beclomethasone, triamcinolone, flunisolide, fluticasone, and budesonide. These drugs can reduce airway inflammation after several months of treatment, but long-term treatment is usually necessary. Long-term use of inhaled corticosteroids has been associated with a good safety profile. High doses of inhaled steroids, for example greater than 1000 mcg/day, are capable of causing hypophyseal–pituitary–adrenal (HPA) axis suppression. Local adverse effects such as hoarseness, dysphonia, cough, and oral candidiasis do occur, but they can usually be avoided by the use of a spacer or holding chamber and by rinsing the mouth after each use. Attempts to reduce dependence on oral corticosteroids should be made, especially by the use of inhaled agents. Asthma in the elderly is often a severe, unrelenting disease, however. While the goal of asthma therapy is always to control the disease without systemic steroids, this is often not possible in the elderly. Side effects of corticosteroid therapy can be quite severe. Attempts should be made to (1) maximize therapy with inhaled steroids, (2) keep oral steroids to the minimum dose possible, (3) use relatively short-acting oral preparations such as prednisone and methylprednisolone, and (4) attempt to control symptoms with alternate-day dosing.

Side effects of chronic steroid therapy are particularly troublesome in the elderly because many of these complications occur in the elderly even without steroid use. Examples are osteoporosis, diabetes mellitus, hypertension, cataracts, and (rarely) depression of immunity and susceptibility to infection. Corticosteroids can aggravate or accelerate these problems. Other complications include myopathy, increased skin fragility, loss of attention span and memory, and mood swings.

Leukotriene-modifying agents (LTMs) are the most recent additions to the list of asthma controllers. There are two subclasses: the 5-lipoxygenase inhibitors, which inhibit the cysteinyl leukotrienes and leukotriene B₄, and the leukotriene D₄ receptor antagonists of the cysteinyl leukotrienes C₄, D₄, and E₄. These agents have been shown to be effective in preventing allergen-induced asthma, exercise-induced asthma, and aspirin-induced bronchospasm. Studies on their use in the elderly are limited. When compared to LTMs, low-dose inhaled corticosteroids are favored. LTMs might also reduce asthma exacerbation rates and the need for steroid bursts [61]. They are generally safe, but rare cases of Churg-Strauss vasculitis have occurred in patients who have severe steroid-dependent asthma and have had a recent steroid taper.

Bronchodilators

Inhaled short-acting β_2 -adrenergic agonists are the treatment of choice for an acute exacerbation of asthma symptoms. Inhaled agents can be delivered by MDIs, dry-powder capsules, and compressor-driven nebulizers. Despite the minimal systemic absorption seen with these agents, slight tachycardia might be observed, which is presumably due to vasodilatation, which results from the stimulation of β_2 receptors in vascular smooth muscle. Tremor might also occur and is especially troublesome in the geriatric patient. Tremor is thought to be caused by stimulation of β_2 receptors in skeletal muscle. In general, however, these drugs have been proven to be safe and effective in all age groups [62].

Long-acting β_2 agonists are helpful for long-term maintenance therapy and can also be used to control nocturnal symptoms. Recent studies of inadequately controlled asthma have shown superior benefit to adding a long-acting β agonist to a moderate-dose inhaled corticosteroid regime rather than doubling the dose of the inhaled corticosteroid, adding theophylline, or adding a leukotriene pathway modifier. Two agents are available, salmeterol and formoterol. Both have a duration of action of 12 hours. Formoterol has the advantage of a more rapid onset of action, similar to the short-acting agents. Salmeterol is available in a dry powder formulation in combination with fluticasone. This gives the advantage of providing bronchodilation with anti-inflammatory benefits. Compliance improves because of prompt relief of symptoms and lower dosing of the inhaled steroid; these benefits are because of the complementary action of the two agents.

The use of regularly scheduled as opposed to as-needed dosing of β_2 -agonists has been associated with diminished control of asthma and heightened bronchial reactivity [63]. There have been reports that asthma medications and particularly β -agonist therapy are contributing to increased morbidity and mortality around the world. Spitzer et al [64] have shown an increased risk of death or near-death from asthma in patients who regularly inhale β -agonist bronchodilators, especially in those who use more than two MDIs per month. It is not clear from this study whether or not heavy use of a β -adrenergic is a marker of severe life-threatening disease or if the heavy use was itself life-threatening. The authors cautioned clinicians about this association and suggested that patients who have heavy β -agonist usage need an immediate re-evaluation of their treatment plans. If the observed increase in mortality is due to the drug, it would have special relevance to the elderly because it has been postulated that at least some excessive deaths are primarily cardiac, and many elderly individuals have occult or recognized coronary disease. Several mechanisms for cardiac toxicity have been outlined by Robin and McCauley [65]. β -agonists cause (1) a dose-dependent drop in serum potassium, and (2) a dose-dependent increase in the QT interval on the electrocardiogram. Because sudden death from ventricular arrhythmia can be caused by both of these mechanisms and it can be a complication of ischemic heart disease, use in the elderly should be closely monitored. Ideally, short-acting β_2 -adrenergic agonists should be prescribed for acute symptom relief on an as-needed basis. The need

for regularly scheduled doses should alert the physician to the need for more intense anti-inflammatory medication.

While there is evidence that β receptor function diminishes with age [20–22], these agents should be used because of their proven track record. The use of other agents such as inhaled ipratropium, which has an excellent safety profile in the elderly [66], should be considered when additional bronchodilator therapy is necessary. Ipratropium has a slower onset of action, requiring 30 to 60 minutes until maximal effect. Inhaled anticholinergic agents produce bronchodilatation by reducing vagal tone. These agents are widely used in patients who have COPD. Their role in long-term maintenance of asthma in the elderly has not been established.

Theophylline is an effective bronchodilator and has some anti-inflammatory properties. Its use has diminished over the past decade because of safety concerns, especially in the elderly [67]. Theophylline is available as a sustained-release preparation that can be taken once or twice a day. Sustained-released formulations of theophylline might be useful as maintenance therapy in moderate and severe persistent asthma for patients who are on inhaled steroid and long-acting β -agonist therapy who are still symptomatic. Theophylline can be used in this setting to either avoid oral corticosteroids or to reduce their dosage. While there is (in general) a steady decline in drug metabolism from early to late adulthood, theophylline clearance does not appear to be sufficiently altered in the elderly to recommend reducing the dose. The narrow therapeutic range of theophylline, frequency of concomitant illnesses that alter theophylline kinetics, and the multitude of drug interactions that affect the clearance of theophylline make it important to closely monitor the blood theophylline level in older asthmatics. Clinical manifestations of theophylline toxicity have been correlated with blood levels of the drug. Life-threatening events can occur with high serum concentrations (>30 mcg/mL) of the drug. These events include seizures and cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia, ventricular ectopy, and ventricular tachycardia. The most common cause for theophylline toxicity is a self-administered increase in medication. There is a step-wise increase in the frequency of life-threatening events caused by theophylline toxicity with advancing age. At comparable theophylline blood levels, patients over age 75 have a 16-fold greater risk of life-threatening events or death than patients under age 25 [68]. The risk of theophylline toxicity can be minimized with careful patient monitoring and education. Monitoring of theophylline blood levels is important to avoid toxicity, especially in the elderly, who are more prone to adverse effects. A range of 8 to 15 mcg/mL is generally considered to be therapeutic.

Inhalation techniques

The inhaled route of asthma therapy is preferred over all therapy because it provides quicker action, fewer side effects, and greater bronchodilatation with

smaller doses of medication. MDIs are the most commonly used method for delivery of bronchodilators and corticosteroids. The great majority of the medication delivered by MDIs is deposited in the oropharynx, with only approximately 10% of the dose delivered to the lungs [69]. Oropharyngeal deposition causes greater systemic absorption, more local irritation, and (for corticosteroids), more likelihood of oropharyngeal candidiasis. The great majority of elderly patients are unable to properly use MDIs, even after proper instruction [70]. Inadequate timing of actuation and inhalation is the most frequent error that is made. Impaired mental function, weakened or deformed hands, and motor or musculoskeletal diseases are other reasons for inadequate MDI use. There are several solutions to this problem. One can deliver short-acting β -agonists, ipratropium, and the inhaled corticosteroid budesonide as aerosolized solutions by pressurized hand-held nebulizers. Alternatively, there is a breath-actuated pressurized MDI that obviates the need to synchronize actuation with inhalation [71]. The use of spacer devices fitted to the mouthpiece of the MDIs has been shown to overcome most of the drawbacks of MDI therapy. Spacers have been shown to decrease oropharyngeal deposition, increase intrapulmonary deposition, improve the pulmonary function of asthmatics who use the conventional MDI inappropriately, and reduce the incidence of oropharyngeal candidiasis [72]. Because drug deposition into the lungs with spacers is greater, the spacers also have the advantage of reducing the number of inhalations of drug needed and, therefore, the cost of drug therapy. MDI use in the elderly patient is highly desirable. Lastly, newer dry powder delivery devices, such as the turbohaler or discus device, which deliver inhaled corticosteroids and long-acting β -agonists have provided simple, easy-to-use preparations that do not require coordination or muscle strength.

Clinical outcome and prognosis

In adulthood, there is a steady incidence of new-onset asthma through all ages, while some with established asthma might develop remission of their disease [73]. Many patients begin with recurrent wheezing following respiratory viral infections. This pattern can gradually or abruptly develop into persistent wheezing and often severe, poorly responsive disease. At other times asthma develops explosively—with no previous respiratory symptoms—immediately following the onset of a typical viral respiratory infection. Longitudinal studies of asthmatic populations have shown that remission from asthma is common in the second decade of life and might be as high as 60% to 70%, but it is much less common in older age groups, occurring only in about 20%. Elderly asthmatics with severe symptoms, long-standing disease, reduced pulmonary function, or a concomitant diagnosis of COPD are much less likely to have a remission. In one 7-year study of 25 elderly (age >70) nonsmoking asthmatics [74], not a single patient went into complete remission, but no one died from asthma. Two patients (8%) died from chronic respiratory insufficiency as if they had cigarette-induced COPD; both had extremely low baseline FEV₁% predicted at entry into the study. Nearly all of the

Table 2
Comparison of asthma in the younger versus elderly patient

	Younger asthmatic	Elderly asthmatic
Symptoms	Mostly intermittent and mild; allergic rhinitis common	Commonly persistent; moderate to severe
Pathophysiology	Atopy common	Mainly intrinsic (non-atopic); begins with viral illness
Provoking agents	Aeroallergens; exercise; viral URI	Viral URI; GI reflux; medication for cardiac disease, glaucoma
Treatment	Intermittent for symptoms; side effects uncommon	Drug utilization high; side effects common
Prognosis	Remission common (60–70%); excellent QOL with therapy	Remission uncommon (20%); healthcare utilization high

Abbreviations: GI, gastrointestinal; QOL, quality of life; URI, upper respiratory tract infection.

patients remained steroid-dependent with persistent symptoms during the study period. These findings were similar to those described by Burrows et al [26] in a community-based survey. Despite severe symptoms and physiologic impairment, most elderly patients who have asthma can lead active, productive lives and do not have a higher death rate because of asthma [75].

Summary

Asthma is common in the elderly population and the differences between younger and older asthmatics should be appreciated (Table 2). Asthma is frequently overlooked in the geriatric population. Objective measures of pulmonary function can aid in a prompt diagnosis and lead to effective treatment and improved quality of life. Because smoking is an important risk factor for asthma-like symptoms of wheezing, cough, and sputum production, asthma is frequently confused with COPD. When airflow obstruction is found, attempts to demonstrate reversibility can uncover an asthmatic component to the disease. In patients who have asthma symptoms and no airflow obstruction, methacholine testing is helpful. When a normal methacholine challenge is present, a diagnosis of asthma can be excluded and the physician can pursue other diagnostic considerations such as heart failure, chronic aspiration syndrome, pulmonary embolic disease, and carcinoma of the lung.

The onset of wheezing, shortness of breath, and cough in an elderly patient is likely to cause concern. Although the adage “all that wheezes is not asthma” is true at any age, it is especially true in the elderly. Diagnosis based on objective measures is essential.

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