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Asthma in the elderly: Diagnosis and management

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The National Asthma Education and Prevention Program's "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma" apply to all ages. This review discusses additional specific points for elderly patients. These patients are very heterogeneous. Their asthma can have begun at any time and can vary greatly in severity. It is frequently associated not only with any of the diseases that affect older persons but also with comorbid lung diseases. Many patients have irreversible airway obstruction, which is due to severe airway remodeling, chronic obstructive pulmonary disease, or bronchiectasis. Diagnosis should include chest radiography and computed tomographic scanning to diagnose other lung diseases if FEV₁ remains low after treatment. Asthma pathogenesis includes not only IgE-mediated allergy but also innate immune inflammation from endotoxin and trypsin-like proteases, and therefore evaluation and control of environmental exposures is an important part of management. Pharmacologic treatment, too, is adjusted to achieve and maintain control and is basically the same for all ages, except that elderly patients have reduced response to bronchodilators and increased side effects from beta adrenergic agonists and glucocorticoids. Many elderly patients have difficulty inhaling aerosols, and therefore nebulizers might be a better delivery system. Oral medications have the benefit of greater ease of administration and greater efficacy on the peripheral airways. Leukotriene antagonists and low-dose theophylline are often helpful additives to aerosol glucocorticoids. Oral glucocorticoids might be indicated for severe asthma. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Asthma, elderly, diagnosis, management, environmental exposures, innate immunity, microbial colonization

As we have learned more about asthma, it has become evident that it is an extremely complex disease that results from the interaction of many different environmental agents on various cells in the airway. This interaction alters the function and expression of many genes. Some of these genes produce the molecules of the complex intracellular pathways that excrete cytokines, chemokines, and adhesion molecules, which attract and activate leukocytes. The result is the airway inflammation and hyperresponsiveness characteristic of asthma.¹ Each person has

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
COPD: Chronic obstructive pulmonary disease
NAEPP: National Asthma Education and Prevention Program
PAR: Protease-activated receptor
SABA: Short-acting β -adrenergic agonist
TLR: Toll-like receptor

both unique genes and a unique exposure to environmental agents at different times and places, which makes the identification and control of a particular patient's problem difficult. Asthma that begins in late adult life is rarely IgE mediated and does not have a familial linkage. There is little, if any, information about specific genetic abnormalities in the elderly. Pharmacologic treatment reduces many of the effects from exposure to environmental agents but, of course, not the exposure itself. Environmental agents can be divided into those suspended in the indoor or outdoor air and those resident in the airways. Airborne agents include pollutants (particles and irritating chemicals), allergens, and stimulants of innate immunity (chiefly bacterial endotoxins and digestive proteases from arthropods and molds). Environmental agents within the airways include respiratory viruses, bacteria, and molds.

The National Asthma Education and Prevention Program (NAEPP)'s "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007¹ and the "NAEPP Working Group Report: Considerations for Diagnosing and Managing Asthma in the Elderly 1996" (National Institutes of Health publication no. 96-3662) are very important documents. This review will not repeat the details in the Guidelines but will focus on issues that pertain particularly to asthma in the elderly. Because each person is unique, management often requires decisions based on logical extension of what is known rather than on large multicenter clinical trials.

SPECIAL CHARACTERISTICS OF ASTHMA IN THE ELDERLY

Lung function decreases with age, and the decrease is greater in men than in women.² The reasons for the decrease include stiffening of the chest wall, reduced respiratory muscle function, and an increase in residual volume from loss of elastic recoil. As a result, elderly asthmatic patients have reduced response to bronchodilators and glucocorticoids. They also have immunosenescence. Naïve T cells decrease, memory T cells increase, and B-cell function decreases, but there is a lesser decrease in innate immunity. Eosinophil function remains the same, but neutrophil numbers increase.

In a study of ovalbumin-sensitized mice, bronchial lavage eosinophil numbers were increased, and lung histology showed greater inflammation and mucus cell metaplasia in aged than in

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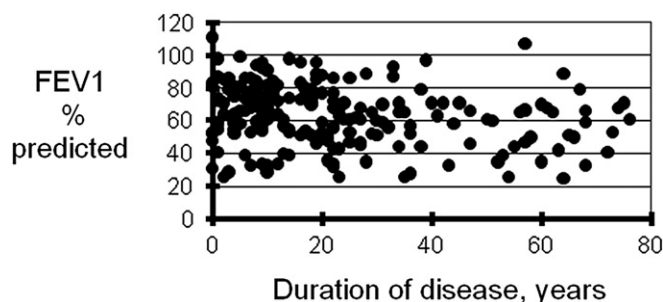


FIG 1. These patients are a random selection of approximately 1,200 patients 65 years of age or older given a diagnosis of asthma at the Mayo Clinic in 1993. The values are the best recorded after inhalation of β -adrenergic bronchodilator and are not necessarily the best that could have been obtained after a course of systemic glucocorticoid treatment. The duration of asthma was dated from the first physician's diagnosis or the first symptoms of wheezing and shortness of breath, whichever came first. There was no difference in the results of patients who received primary care at Mayo Clinic and those referred from other cities. Only 32% of these patients had FEV₁ after bronchodilator of greater than 60% of predicted normal value, and 20% had FEV₁ of less than 50% of predicted normal value. Reprinted with permission from Reed.⁵

young mice.³ However, the increase in airway hyperreactivity was significantly less. Antigen exposure produced a different cytokine profile in older mice (increased IFN- α and IL-5 levels) compared with that seen in young mice (increased IL-4 and IL-1 levels).

Asthma that begins in children and adults younger than 40 years is usually IgE mediated, and exacerbations are typically precipitated by exposure to allergens or by acute respiratory tract viral infections. However, asthma beginning later in life is rarely IgE mediated, and in the elderly it often develops with a component of irreversible airway obstruction.⁴ Fig 1 shows 3 important characteristics of asthma in the elderly.⁵ First, and perhaps most importantly, is that there is great variability in the duration and severity of the disease. Second, the onset can have been at any time since childhood but more often begins in middle age or later. Third, many of these patients have severe irreversible obstruction unrelated to the duration of the disease. Not shown in Fig 1 is that the degree of irreversible obstruction was unrelated to pack-years of cigarette smoking, suggesting that there are additional causes.

Studies with computed tomography have identified 3 main reasons for the irreversibility.⁶⁻⁹ The first is airway remodeling, which is greater with more severe disease.¹⁰ Remodeling not only includes widespread thickening of the basement membrane and hypertrophy of smooth muscle but also hypertrophy of submucous glands in some central cartilaginous airways that can cause localized, even complete, obstruction in the affected bronchial segment (Fig 2). It is significant that proteases from neutrophils (elastase) and mast cells (chymase) stimulate mucus secretion.¹¹ However, the growth factors and intracellular pathways of submucous gland hypertrophy are as yet poorly defined. The second reason for irreversibility is coexisting chronic obstructive pulmonary disease (COPD), and the third is bronchiectasis with segmental pulmonary fibrosis. The bronchiectasis in some patients is central and cylindrical, like allergic bronchopulmonary aspergillosis (ABPA). (Indeed, it probably is ABPA.) In others it is peripheral and often multiple.

After almost 100 years since Rackemann and Cooke debated whether nonallergic asthma should be called "intrinsic" or

"infectious," the pathogenesis is becoming clear. Innate immune pathways provoke non-IgE-mediated airway hyperresponsiveness and eosinophilic inflammation.¹² The cell biology is complex. Briefly, there are 2 types of innate immunity: T_H1-like innate immunity, which is directed against unicellular microorganisms, and T_H2-like innate immunity, which is directed against multicellular organisms (parasites, arthropods, and molds). T_H1-like innate immunity results from the interaction of bacterial and viral molecules with ligands on cell membranes. In airway disease the most important external agent is bacterial endotoxin, which stimulates Toll-like receptor (TLR) 4. Stimulation of TLR-4 results in neutrophilic inflammation and increased IgG antibody production to concomitantly administered antigens. Stimulation of TLR-2 by β -(1,3) glucans from fungal cell walls generates T_H2-type cytokines.¹³ T_H2-like innate immunity also results from the stimulation of protease-activated receptors (PARs), especially PAR-2, by serine and cysteine digestive proteases from multicellular organisms, particularly mites and fungi. Thrombin and proteases from inflammatory cells, especially mast cell tryptase and chymase, also stimulate PARs. This stimulation results in attraction and activation of eosinophils and neutrophils, degranulation of eosinophils and mast cells, increased response of afferent neurons, smooth muscle contraction and hypertrophy, angiogenesis, and fibrosis.¹⁴⁻¹⁶ Stimulation of PAR-2 results in increased IgE antibody production to concomitantly administered antigens.¹⁷ PAR-2 is overexpressed on the airway epithelial cells of patients with asthma and allergic rhinitis.^{18,19} Thus there is a strong probability that PAR-2 innate immunity is the mechanism of "intrinsic" asthma. The details of the association between asthmatic inflammation and exposure to environmental agents that stimulate these innate immune intracellular and intercellular pathways are still incompletely defined, particularly correlation with location, amount, and duration of exposure. The genetics, and more importantly the epigenetics, of these reactions remain to be investigated. For example, it is not known whether the increased expression of PAR-2 on epithelial cells is the result of the airway inflammation or is present before the inflammation develops, and of course, asthma from adaptive IgE immunity and innate immunity are not mutually exclusive.

Coexistence of asthma and COPD in elderly patients is not only due to cigarette smoking.²⁰ Rene Laennec²¹ described emphysema almost 2 centuries ago, long before cigarettes were invented. Exposure to airborne endotoxin causes COPD in many occupations in which there is exposure to organic dusts, such as grain dust, cotton dust, barn dust, and drying tobacco dust, or in which contaminated water becomes aerosolized. Endotoxin is present also in the dust and air of many dwellings and is a factor in the development and severity of asthma.^{22,23} Also, it is one of the many toxic components of cigarette smoke.^{24,25} Hogg²⁶ has reported that latent adenovirus in respiratory epithelial cells is the reason that COPD develops in some smokers but not in others. Adenovirus increases the airway response to endotoxin and reduces the anti-inflammatory effects of glucocorticoids in allergic lung inflammation.^{21,27-29} Macek et al³⁰ suggest that latent viral infection might also be a factor in the development of asthma, but they found the presence of latent viruses in epithelial cells of asthmatic patients to be no different from that seen in nonasthmatic subjects. Perhaps patients with asthma respond differently.

Interpretation of data about the epidemiology of asthma, especially asthma in the elderly, is handicapped by the difficulty

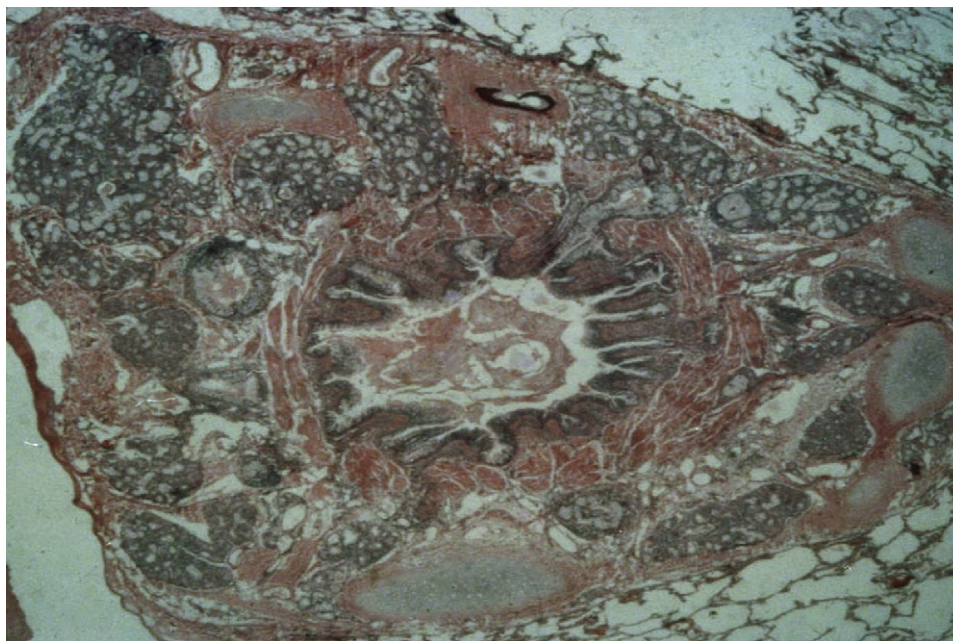


FIG 2. Pathologic specimen from a fatal case of asthma. Note the complete obstruction of a cartilaginous bronchus by a mucus plug and the hypertrophy of the mucous glands.

of identifying appropriate subjects. Most studies are based on physicians' diagnoses or on patients' recollections. Physicians are often reluctant to make the diagnosis, and the accuracy has varied over time and in different locations. Another difficulty is that many epidemiologic studies, particularly prospective studies, include subjects who have only asthma and exclude those who have coexisting lung diseases. Accepting these limitations, there are several important conclusions about the epidemiology of asthma in the elderly.

The incidence rate of asthma is much higher in children than adults, but after age 15 years, it remains at about 1/1,000 per year.³¹ The prevalence in the elderly is similar to the prevalence in all adults, about 5% to 10%. Asthma might have persisted from early years or had its onset at any time, even late in life. Asthma that persists from youth remains relatively stable, but asthma beginning in the elderly is more severe and progressive and less reversible.³² It is more common in women than in men.

Data about death from asthma are conflicting. Death certificates are often inaccurate.³³⁻³⁵ In Denmark the death rate was higher than in control subjects, but in a Minnesota community-based study the mortality rate of patients with asthma increased with age at a rate similar to the general population.^{36,37} The chief difference was that patients with asthma were more likely than nonasthmatic subjects to die of lung diseases. However, patients with intrinsic asthma have a higher rate of decrease in lung function and are more likely to die of asthma than patients with allergic asthma,^{37,38} and the death rate is higher in poor and minority populations.³⁹ Death in elderly patients is seasonal, occurring most often in December through February.^{38,40} This is presumably due to respiratory tract infections.

DIAGNOSIS

The NAEPP Expert Panel 3 Guidelines stress 2 key points for the diagnosis of asthma¹:

- To establish a diagnosis of asthma, the clinician should determine that (1) episodic symptoms of airflow obstruction or airway hyperresponsiveness are present, (2) airflow obstruction is at least partially reversible, and (3) alternate diagnoses are excluded.
- Recommended methods to establish the diagnosis are (1) a detailed medical history; (2) a physical examination focusing on the upper respiratory tract, chest, and skin; and (3) spirometry to demonstrate obstruction and assess reversibility. Reversibility is determined by an increase in FEV₁ of 12% or greater from the baseline value or by an increase of 10% or greater of predicted FEV₁ after inhalation of a short-acting bronchodilator. Finally, additional studies should be performed as necessary to exclude alternate diagnoses.

In the elderly there is an additional key point to consider: the diagnosis of coexisting lung disease in subjects whose FEV₁ remains less than 60% of predicted normal value after inhaling a bronchodilator. There are 3 main reasons for the irreversibility: severe airway remodeling, emphysema, and bronchiectasis with segmental fibrosis.

A history of nocturnal symptoms is useful in patients who also have COPD to establish the diagnosis of asthma in elderly patients. The history and physical examination should include the upper airway, particularly sinusitis and polyps. Enquiries should be made about adverse drug reactions, particularly aspirin and α -adrenergic blockers and angiotensin-converting enzyme inhibitors. Elderly asthmatic patients typically have additional medical problems, and therefore it is especially important that the medical evaluation includes these other diseases, particularly coronary artery disease, hypertension, diabetes, impairment of mobility and independence, and Alzheimer disease. In taking the history, it is important to consider the duration of the disease in elderly patients because asthma that has persisted from an early age is likely to have allergic components, including occupational

TABLE I. Diagnostic details that affect management after the diagnosis of asthma has been established

Age at onset
Total and specific IgE levels
Pack-years of cigarette smoking or passive exposure
Past or present occupational exposures
Upper airway disease, sinusitis, and polyps
Aspirin sensitivity
β -Adrenergic blocking drugs, including eyedrops, and angiotensin-converting enzyme inhibitors
Persistent airway obstruction despite therapy
Abnormal chest radiographic or computed tomographic scan results
Domestic exposures to irritants, allergens, and stimulants of innate immunity
Coexisting diseases

exposures. Also, cigarette smoking or past occupational exposure to airborne endotoxin might have induced coexisting COPD. It is also important to consider not only pack-years of cigarette smoking but also passive exposure. A history of recurrent episodes of pneumonia suggests bronchiectasis, including bronchopulmonary aspergillosis.

Spirometry to demonstrate obstruction and assess reversibility is an essential part of the diagnosis unless, of course, the elderly patient is unable to do it. Increase in FEV₁ of at least 12% after inhalation of a short-acting α -adrenergic bronchodilator is a key point of the diagnosis of asthma. Bronchoprovocation tests are very rarely indicated. If the obstruction is severe and not fully reversible, additional lung function tests are needed. Measurement of lung volumes and CO diffusing capacity can help identify coexisting diseases. Repeating the spirometry after 2 weeks of treatment with systemic glucocorticoids will determine the patient's "personal best" by reversing severe asthmatic obstruction. This is also important in setting the criteria for control of the patient's asthma.

Blood and sputum eosinophilia are important components of the diagnosis, but eosinophilia might be suppressed by effective aerosol glucocorticoid treatment. Measurement of total and specific IgE is valuable. Elderly asthmatic patients have increased serum IgE levels, even without specific IgE to allergens, and it is desirable to check for specific IgE antibodies because even though the history does not suggest allergic reactions, allergy might be a factor. Also, negative test results are helpful in planning the management.

All elderly patients should have a chest radiograph to reveal additional lung diseases; asthma does not protect against cancer.⁴¹ In patients with severe irreversible obstruction, computed tomography is indicated to define the pathology.

After the diagnosis of asthma is established, the history should include details of possible exposures to environmental agents in the home. Such exposures depend on location; for example, hot humid Houston differs from cool dry Denver, and in New York City exposures in apartments on Park Avenue differ from those in Harlem or single-family houses in Westchester. The main things to consider and control are pets, mice, cockroaches, mites, molds, water damage, and contaminated humidifiers and heating/air-conditioning ducts. These things are not only sources of allergens but also endotoxins and trypsin-like proteases that stimulate innate immune inflammation. Exposure to irritants and volatile organic compounds is also important.

TABLE II. Details of asthma control important in elderly patients

Monitor skill of inhaling aerosol medications
Control exposure to environmental agents
Establish "personal best" FEV ₁
Add oral medications, such as leukotriene antagonists or low-dose theophylline, for patients with severe asthma
If there is a concern about cardiotoxicity of β -adrenergic agonists, substitute anticholinergic aerosols
Manage osteoporosis and other coexisting diseases
Influenza and pneumococcal immunization

At the present time, the history is the most practical means of identifying exposures. Quantitative measurement of outdoor air pollutants is a standard procedure of the Environmental Protection Agency. Application of this principle has been useful to identify and control exposure to allergens and endotoxin in many occupational settings and has been applied in the home.⁴²

Assays for the important allergens, endotoxin, and proteases are available. However, they are limited to research laboratories. There are still some uncertainties as to how to collect the sample and express the results. Some particles, such as house dust mite allergens, settle so rapidly that air sampling is unreliable, and therefore dust collections are appropriate. But where and how should the dust sample be collected? If the results are expressed as milligrams per gram, they might be skewed by the amount of inert dust in the sample. Expression as milligrams per square meter is more representative. Allergic asthma correlates with the concentration of allergen in the home.⁴² In addition, a national study of endotoxin and allergen concentrations in various locations in the home reported correlation with endotoxin exposure and prevalence of asthma.²³ The correlation was higher in adults than in children. Endotoxin concentration was greatest in the kitchen and family room and did not correlate with mite and animal allergens (Table I).

MANAGEMENT

The NAEPP's Expert Panel Report 3 guidelines are organized around 4 essential components of asthma management:

- measures of assessment and monitoring obtained by using objective tests, physical examination, patient history, and patient report to diagnose and assess the characteristics and severity of asthma and to monitor whether asthma control is achieved and maintained;
- education for a partnership in asthma care;
- control of environmental factors and comorbid conditions that affect asthma; and
- pharmacologic therapy.

These 4 components apply equally to all ages. For the elderly, the 2 that include particular points to consider are control of environmental factors and comorbid conditions and pharmacologic therapy.

Control of environmental factors obviously depends on which factors are present at the patient's location. When outdoor air pollutants and allergens are prevalent, the patient should be advised to stay indoors. Detailed information for patients about identification and control of indoor allergens has been prepared by a partnership between the Allergy Foundation of America and Allergy Standards Limited and is available at www.asthmaandallergyfriendly.com. This document is a valuable

component of the education for partnership in asthma care. The information will aid in identifying the particular problems in the patient's own home, and following these recommendations will not only control allergens but also irritants and endotoxin and protease stimulants of innate immunity. Of course, recommendations must include a smoking cessation program.

Control of environmental agents resident within the airways has received little attention. *Pseudomonas* species, a source of endotoxin, is often present in patients with COPD. In asthmatic patients with bronchiectasis, control of the infection is obviously important. If the bronchiectasis is ABPA, antifungal drugs are effective in addition to oral glucocorticoids.^{43,44} Antifungal treatment is also effective for late-onset asthma and severe asthma with fungal sensitization.^{45,46} Fungal colonization of the upper airway is often present in patients with polypoid rhinosinusitis.⁴⁷ However, the identification of affected patients and treatment with antifungal agents is controversial.⁴⁸

The role of fungal colonization of the bronchial tree has only been investigated for ABPA, and more information is needed. Years ago, when establishing diagnostic criteria for ABPA at the Mayo Clinic, I found sputum culture to be very sensitive; only 1 patient had a negative result. However, it was not as specific; results for the culture for *Aspergillus* species were positive in a third of the control group of patients with asthma severe enough to produce a sputum sample. Localized fungal germination generating an innate immune response could explain the localized airway obstruction shown in Fig 2. Antifungal treatment of asthma has been found to improve the quality of life.⁴⁹

Identification and control of the coexisting diseases of the airways, rhinosinusitis, bronchiectasis, and COPD, is a key point of management in the elderly. Control of other diseases will depend on the condition, and therefore the details are beyond the scope of this review.

The principles of pharmacologic treatment are similar for all ages. Therapy with aerosols, especially aerosol glucocorticoids, has special problems in the elderly. Many cannot inhale them effectively. Careful instruction is essential, and on each visit, the patient's skill in inhaling the medication must be reviewed. Many find dry-powder inhalers easier to use, but some might not be able to inhale rapidly enough to aerosolize the powder. In such cases a nebulizer might be necessary. Another problem with aerosol delivery is that it might not provide sufficient concentration in the peripheral airways. Thus in severe cases systemic glucocorticoids might be indicated. In the elderly osteoporosis and hyperglycemia are the major side effects, and therefore appropriate management of osteoporosis is important. Alternate oral medications include leukotriene modifiers, which are particularly effective in aspirin-sensitive patients, and low-dose theophylline. Bronchodilating doses of theophylline of 10 to 20 mg/L that act through phosphodiesterase and adenosine A₂ pathways are hazardous in the elderly, but lower concentrations of 5 to 10 mg/L that act through histone deacetylases have substantial anti-inflammatory effects by inhibiting the production of the notorious nuclear factor κ B.⁵⁰ Theophylline is not only effective for controlling the inflammation of asthma but also for COPD.⁵¹ The advantages of oral administration, suppressive effect on neutrophils, and synergy with aerosol glucocorticoids make it an especially practical treatment in the elderly. Long-acting β -adrenergic agonists have become controversial because patients with coronary artery disease are vulnerable to the adverse effects, although published data indicate that they are

safe.⁵²⁻⁵⁴ The plus side is that they increase the anti-inflammatory effect of glucocorticoids. Overdosing with short-acting β -adrenergic agonists (SABAs) is cardiotoxic. Aerosol anticholinergic agents are a practical substitute for β -agonists and might even increase their effectiveness if administered together.⁵⁵ One of the reasons that they have not been used more frequently for asthma is that some younger adults do not respond even to large doses. It is not clear whether this is true for elderly patients, and therefore it is prudent to check their efficacy with spirometry. Anticholinergic agents also increase the anti-inflammatory effect of glucocorticoids.⁵⁶

The Expert Panel Report 3 recommendations for management of acute episodes in the hospital or urgent care setting apply to the elderly. The only points to stress are to avoid the cardiotoxic effects of SABAs and provide oxygen. Because most of these episodes are due to respiratory tract infection and some might be fatal, it is critical to immunize for influenza yearly and for pneumococcus at least every 5 years. Respiratory syncytial virus causing inflammation through TLR-4 is as important in the elderly as in children.

SUMMARY

Asthma in elderly patients presents special problems for clinicians. Individual patients vary greatly in terms of severity, pathogenesis, and environmental provoking agents and especially in complicating additional lung diseases. The associated lung diseases include emphysema, bronchiectasis, and even carcinoma. Asthma that begins late in life often has a major component of irreversibility from these other diseases. Other diseases of the elderly, especially coronary artery disease, hypertension, diabetes, and Alzheimer disease, make the management more difficult.

Appropriate carefully individualized management to maintain control follows the NAEPP's Expert Panel Report 3 guidelines. There are 4 special points. First, evaluate and reduce environmental exposures, including stimuli of innate immunity. Second, be sure that the patient is inhaling aerosol glucocorticoids effectively. Oral medications are useful additions to aerosols. Antifungal drugs are useful in patients with fungi colonizing the airways. Third, consider side effects of medications, such as aspirin, β -adrenergic blockers (including eyedrops), angiotensin-converting enzyme inhibitors, and also the medications prescribed for asthma. Finally, diagnose and manage associated lung diseases that are contributing to the severity of the patient's problem.

What do we know?

- "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma" apply with a few special points for elderly patients.
- Diagnosis and management must be individualized.
- The disease is highly variable in age of onset, severity, and presence of additional lung diseases, chiefly COPD and bronchiectasis.
- All patients have increased serum IgE levels, even those with intrinsic asthma with onset late in life.
- The airway obstruction is frequently incompletely reversible, either because of severe remodeling or the additional diseases.

- Chest radiography and in some cases computed tomographic scanning is indicated to identify these additional diseases and even carcinoma.
- The presence of nocturnal symptoms and eosinophilia helps confirm the diagnosis in patients with coexisting COPD.
- Evaluation and remediation of environmental exposures, including stimuli of innate immunity, is an important but often overlooked part of control.
- Some elderly patients cannot inhale aerosol medications effectively.
- Oral medications, including low anti-inflammatory doses of theophylline, are useful additions to aerosol glucocorticoids, especially in treating peripheral airways.
- Overdose with SABAs or oral glucocorticoids can cause serious side effects.
- Long-acting β -adrenergic agonist can have cardiotoxic effects in patients with heart disease. Aerosol anticholinergic agents can be an alternative. Both increase the anti-inflammatory effects of glucocorticoids.

What is still unknown?

- The genetics and especially the epigenetics of asthma in the elderly: Do they differ from those of younger adults?
- Does chronic viral infection of the respiratory epithelium influence the pathogenesis?
- Why are some segmental airways more affected than others?
- Does localized germination of *Aspergillus* species or similar molds account for this?
- What is the cell biology of submucous gland hypertrophy?
- Would quantitative measurements help evaluate a patient's home environmental exposure?
- If so, what is the best way to collect and analyze the sample?

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