Advances in Therapy for Adult Asthma

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There are >22 million Americans with asthma. Chronic asthma is a worldwide problem with an increasing socioeconomic burden on individuals and on society. Recent advances have been made in diagnostic lung imaging, defining control of asthma, as well as in the education of patients with asthma. Accurate diagnosis of the cause of chronic cough in adults and of asthma in elderly individuals will help affected individuals receive appropriate treatment. Inhaled corticosteroids are the recommended first-line therapy for persistent asthma and can help prevent exacerbations in patients with asthma that are not well controlled. Early intervention and improved management can significantly reduce the socioeconomic burden of asthma. Patient education is an essential part of asthma management. (*Clinical Cornerstone*. 2007;8[4]62–75) © 2008 Excerpta Medica Inc.

Asthma is a chronic inflammatory disorder of the airways that affects people of all ages. It is associated with recurrent exacerbations and is one of the most common chronic diseases worldwide. The prevalence and socioeconomic burden of asthma increased dramatically over the past 2 decades, although asthma deaths and hospitalizations have stabilized in the last few years, possibly reflecting better recognition and disease management.[1,2] Direct US health care costs attributed to asthma totaled $14.7 billion in 2007, with prescription drugs being the largest single direct medical expenditure. Indirect costs attributed to asthma totaled another $5 billion, with lost productivity being the largest single indirect medical expenditure.[1] Patients whose asthma is not well controlled have much higher health care costs than patients whose asthma is well controlled, with 4% of all patients with asthma using 50% of all asthma dollars.[3]

Over 32 million Americans, or 112 per 1000, have been diagnosed with asthma by a health care professional some time during their life,[1] and >22 million Americans currently have asthma.[4] Children ages 5 to 17 years have the highest asthma prevalence rates; in 2005, 142.2 per 1000 children ages 5 to 17 years had been diagnosed with asthma in their lifetime.[1] In 2005, females were ~18% more likely than males to have been diagnosed with asthma some time during their life, and blacks were 26.4% more likely than whites to be diagnosed with asthma.[1] Gender prevalence trends, however, vary with age. Among children under 18 years of age, males are 28% more likely than females to currently have asthma, but among adults over 18 years of age, females are 78.2% more likely than males to have asthma.[1]

Asthma can significantly affect quality of life. Morbidity due to asthma is related to the severity of the disease, undertreatment with anti-inflammatory agents, overreliance on bronchodilators, and delay in seeking medical help during an exacerbation.[2] In 2004, the age-adjusted death rate from asthma was 1.3 per 100,000, and in 2003 there was an 80% greater death rate in females than males, and a more than double rate in blacks compared with whites.[1]

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Asthma most commonly begins in childhood but can persist (or recur) into adulthood or have its onset in adulthood. Risk factors for asthma include host factors, such as genetic predisposition, gender, and race; and environmental factors, such as viral and bacterial infections, or exposure to secondhand smoke, cockroaches, pollen,

dust mites, molds, pets and other animals, nitrogen dioxide, and air pollution. Some of these triggers are found more frequently in certain geographic areas.[5] Environmental factors can exacerbate asthma and/or influence a predisposed individual's susceptibility to developing asthma.

The course of asthma varies considerably in different patients. Some patients recover completely or have long remissions with mild relapses. Other patients get worse, develop irreversible airway obstruction, or even die, often suddenly. Asthma may be more accurately considered a syndrome, or multiple overlapping syndromes, with many etiologies that affect outcomes differently, rather than a single disease with a single underlying etiology.[6,7]

Based on studies of the natural history of asthma, Reed[6] suggested classifying asthma syndromes as: (1) intermittent wheezing with respiratory infection in infants; (2) immunoglobulin E–mediated asthma, usually developing during the first 2 decades of life; (3) intrinsic asthma developing at all ages; and (4) asthma associated with other chronic lung diseases. Wheezing in infancy progresses in about one third of children into diagnosed asthma by the time the child is school-aged, and severity of chronic asthma is stable throughout adolescence. Allergic asthma can be mild or severe and may or may not progress. To some extent, severity is determined by the amount and duration of exposure to the allergen(s). Intrinsic asthma appears more frequently in middle-aged and older adults, is more likely to be persistent, and can progress in severity.

A greater understanding of asthma phenotypes and the effect of the environment on expression of these phenotypes should further understanding of the pathogenesis of asthma and lead to improved diagnostic and preventative approaches.[8,9] Although allergic and nonallergic asthma are probably the most common phenotypes described, others have classified asthma phenotypes into 3 broad categories: (1) clinical or physiological phenotypes, which include those defined by level of severity, frequency of exacerbations, the presence of chronic airflow restriction, the age of asthma onset, and resistance to steroids; (2) phenotypes defined by their relationship to specific triggers, such as exercise, environmental allergens, occupational allergens or irritants, drugs, and menses; and (3) phenotypes categorized by their immunopathology on the basis of inflammation, especially of inflammatory cell types, such as eosinophils or neutrophils.[7] Allergic sensitization that triggers asthma is probably the largest overall phenotype, but substantial overlap between phenotypes exists. Therapeutic approaches targeted to specific types of asthma should improve treatment outcomes.

Most patients with asthma have mild to moderate disease that is controlled by a combination of anti-inflammatory drugs and β_2-agonists. However, about 10% of patients with asthma have symptomatic asthma despite treatment.[9] Patients with asthma that is resistant to treatment have the greatest impairment of lifestyle and account for a substantial portion of health care costs related to asthma management.[10] Further, many patients with severe asthma do not receive adequate treatment because they are misdiagnosed, underdiagnosed, undertreated, or adhere poorly to treatment.

Early intervention and improved management can significantly reduce the socioeconomic burden of asthma. Patient education is an essential part of asthma management. Effective patient education involves a partnership between the patient and health professional, with information clearly communicated and frequent revision and reinforcement of information.[2]

ADVANCES IN ADULT ASTHMA

In the past few years, several advances in the understanding of physiology, epidemiology, and therapy for adult asthma have been made.[8] Progress has been made in elucidating genetic mechanisms for asthma and the interaction of genes with the environment. Chromosomal linkage regions and several candidate genes have been identified, including a gene associated with asthma and bronchial hyperresponsiveness. A better understanding of the linkage between the upper and lower airways in allergic asthma and allergic rhinitis was also gained. New immune-modulating pharmaceuticals have entered the marketplace, as well as introduction of the humanized monoclonal anti-IgE antibody, omalizumab, for treatment of allergic asthma.

One recent advance in adult asthma involves innovations in lung imaging. Imaging of the ventilated air spaces of the lung has been challenging, but such imaging should improve understanding of the pathology of asthma. Conventional pulmonary function tests are the most commonly used noninvasive method to assess diffuse lung disease. These tests, however, only provide one overall assessment that represents all airways and cannot assess individual airway variations. Being able to view individual airway responses to stimuli, treatments, and

changes in lung volume would aid understanding of airway pathophysiology in asthma.[11]

High-resolution computed tomography (HRCT) is now widely accepted as a diagnostic and investigational radiological tool for evaluation of airway function.[11] HRCT is uniquely capable of imaging and quantifying changes in airway size at different lung volumes that are not detectable by conventional global lung measurements. HRCT uses thin slices, high spatial frequency reconstruction algorithms, and a small field of view to resolve the anatomical detail of pulmonary structures as small as 200 µm. Unlike other pulmonary measurement techniques, HRCT can be used to make repeated airway luminal and wall thickness measurements of multiple individual airways at different lung volumes.

Using HRCT, Brown[11] has shown that distention of the airways though deep inspiration plays a major role in maintaining airway patency in healthy individuals, and that limited distension of the airways may be a factor in individuals with asthma. When healthy individuals refrain from taking any deep inspirations, airway obstruction can be induced with an inhaled spasmogen, but when deep inspirations are taken before the inhalation challenge, no obstruction occurs. However, when individuals with asthma refrain from or take a deep inspiration, their inducible reactivity does not change, perhaps because a deep inspiration may be unable to stretch the airways due to increased airway tone compared with healthy individuals.[11]

Trampel et al[12] presented a new method of diffusion imaging of the lung, diffusional kurtosis imaging (DKI) that is sensitive to changes in the bronchi and bronchioles. Conventional diffusion magnetic resonance imaging (MRI) using inhaled hyperpolarized gas is an alternative to HRCT for pulmonary imaging. However, MRI of hyperpolarized noble gases is only capable of monitoring diffusion over short times and distances, and is therefore only sensitive to changes in the small structures of the lung, mainly the alveoli. DKI quantifies diffusion over relatively large distances and can be used to assess bronchiolar rather than alveolar diameter. Preliminary DKI measurements on 4 healthy individuals and 1 individual with asthma showed similar apparent diffusion coefficients in all subjects, but markedly reduced DKI in the subject with asthma.[12]

In addition to advances in lung imaging, progress has also been made recently in the education of patients with asthma. Good asthma care requires a sufficient number of trained health care professionals available to patients with asthma, guidelines on asthma management that can be adapted for local use, education for the health care professional regarding asthma guidelines, a partnership between the health professional and patient to guide patient self-management, and use of written action plans to enhance patient adherence and earlier recognition of exacerbations.[2]

The Global Initiative for Asthma was created to increase awareness of asthma among health care professionals and the general public and to improve prevention and management of asthma. It offers a framework for asthma management that can be adapted to local use, and includes pocket guides for asthma management and prevention for health professionals.[2,13,14] Despite progress, misdiagnosis or underdiagnosis of asthma is still common, as is patient noncompliance with preventive therapies recommended by health care professionals.[2]

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Influenza infection is frequently associated with asthma exacerbations, but the influenza vaccine itself has a limited potential to trigger asthma exacerbations. In the past, influenza vaccination has been recommended for persons who have risk factors for complications of infection, including persons with asthma.[15] A review of inactivated influenza vaccine concluded the vaccine was safe to administer to children and adults with asthma, including those with severe asthma.[16] However, live attenuated influenza vaccines have recently become available. Some researchers conclude these are more effective, easier to administer, and safe for patients with asthma.[17] The Advisory Committee on Immunization Practices of the US Centers for Disease Control, however, recommends that inactivated, rather than live attenuated, influenza vaccine be used for children and adults

with asthma.[18] According to the guidelines published in August 2007 by the National Heart, Lung, and Blood Institute (NHLBI),[4] clinicians are encouraged to consider inactivated influenza vaccination for patients who have asthma; administration of this vaccine to children >6 months of age and adults is regarded as safe. However, the NHLBI report noted that the vaccine should not be given with the expectation that it will reduce either the frequency or severity of asthma exacerbations during the influenza season but because persons who have asthma are considered to be at risk for complications from influenza.[4]

DIFFERENTIAL DIAGNOSIS OF CHRONIC COUGH IN ADULTS

Chronic cough is a common problem and a major cause of morbidity in adult populations.[19] In specialized cough centers that treat patients whose cough has lasted more than 8 weeks, asthma has been identified as 1 of the 3 most common causes of chronic coughing, along with gastroesophageal reflux disease and postnasal drip syndrome.[20] In a review of 13 studies including a total of 317 patients with chronic cough referred to specialized cough centers, a mean of 25% of patients were found to have asthma (range 6%–59% across clinics), 20% esophageal disease, and 34% rhinitis.[20] Other causes of chronic cough include treatment with angiotensin-converting enzyme (ACE) inhibitors, a history of cigarette smoking, chronic bronchitis, cystic fibrosis, infection, foreign body, or autoimmune disorders.[20] A small group of patients with chronic cough may also have chronic idiopathic cough, characterized by an upper respiratory tract infection that triggers the initial cough, and sensitive cough reflexes.[21]

Clinical history and examination of the patients with chronic cough should include history of smoking, ACE-inhibitor therapy, upper respiratory infection, and mucopurulent secretions.[20] Wheezing, chest tightness, and dyspnea in the absence of any of the above suggest asthma, although some patients with asthma have only cough. A history of nasal congestion, sneezing, purulent nasal discharge, or postnasal drip suggests rhinitis. A history of heartburn or cough after meals, during eating, or while supine suggests esophageal disease.

In some patients with asthma, chronic cough is the main or only symptom, referred to as cough variant asthma.[2,20] Coughing may also occur only at night, with normal daytime evaluations. For these patients, measurement of hyperresponsiveness and the variability of lung function as well as documentation of sputum eosinophils are important, although not often done in clinical practice. Some patients with chronic cough may have sputum eosinophils present but have normal lung function.[2] Treatment similar to that used in patients with more typical asthma, such as initiation of bronchodilators and corticosteroids, usually improves cough within 1 week and resolves cough within 8 weeks.[20]

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DIAGNOSTIC MISCLASSIFICATION IN THE ELDERLY

The incidence of asthma in elderly individuals is similar to that in younger adults, but asthma is more likely to progress in severity with age.[6] Asthma in the elderly is associated with a lower quality of life and considerable morbidity, yet the diagnosis of asthma in elderly patients is often missed.[22] Elderly patients may also be less compliant about asthma treatment due to unique factors, such as comorbid conditions and reimbursement issues. Perception of the symptoms and severity of asthma may also be reduced in elderly individuals because of long-term adaptation, further confounding diagnosis and treatment. Thus, elderly individuals with asthma are frequently underdiagnosed and undertreated.

Elderly patients are more likely to be misclassified than younger patients because they may be unable to perform valid tests of lung function and because of the presence of other diseases that make diagnosis of asthma more complex. Elderly individuals often have lung damage from smoking or long-term exposure to environmental allergens or irritants. Coexisting lung disease, such as bronchiectasis with fibrosis and chronic obstructive pulmonary disease (COPD) with emphysema, also cause irreversible airway obstruction.[6] COPD associated with a

long history of smoking may have an inflammatory component that marginally responds to anti-inflammatory drugs. Improvement in lung function and symptoms with a trial of oral corticosteroids usually confirms asthma as a cause of chronic respiratory symptoms.[2] Diagnostic features helpful in differentiating asthma from other diseases in elderly individuals are shown in the **table**.[23]

TREATMENT COMPLICATIONS AND ASTHMA CONTROL IN PATIENTS WITH COMORBIDITIES

Comorbidities are common in adults with asthma. In a study of 2952 Finnish subjects with asthma, 63% reported also having other diseases in addition to other chronic pulmonary diseases and allergies, with musculoskeletal and cardiovascular disorders being most common.[24] About 65% of subjects took other prescription medicines in addition to asthma medications, and 41% of all subjects and 21% of young adults took at least 5 prescription medicines concomitantly. Comorbid conditions and their medical therapies may complicate adherence to asthma treatment and interfere with asthma control.

TABLE. DIFFERENTIAL DIAGNOSIS OF ASTHMA IN ELDERLY INDIVIDUALS.

Diagnosis	Diagnostic Features
Asthma	Early onset Varying symptoms Symptoms during the night/early morning Presence of allergy, rhinitis and/or eczema Family history Airflow limitation that is largely reversible
Bronchiectasis	Large volume of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Bronchial dilation and bronchial wall thickening on chest radiography/CT
Congestive heart failure	Fine basilar crackles on auscultation Dilated heart on chest radiography Pulmonary edema Volume restriction not airflow limitation on pulmonary function tests
COPD	Midlife onset Slowly progressing symptoms Long history of smoking

CT = computed tomography; COPD = chronic obstructive pulmonary disease.
Adapted with permission.[23]

Coronary Artery Disease

β_2-Agonists are commonly used in patients with asthma and COPD. The effects of β_2-agonists, however, oppose those of β-blockers, which are commonly used in individuals with cardiac disease. β_2-Agonist use has been associated with an increased risk of myocardial infarction, congestive heart failure, cardiac arrest, and sudden cardiac death.[25] In a meta-analysis of randomized, placebo-controlled trials of β_2-agonist treatment in patients with obstructive airway disease, β_2-agonist use significantly increased the risk for a cardiovascular event (relative risk [RR] 2.54; 95% CI, 1.59 to 4.05) compared with placebo. The RR for sinus tachycardia alone was 3.06 (95% CI, 1.70 to 5.50).[26] β_2-Agonists increase heart rate, contractile force, and cardiac output; and decrease peripheral vascular resistance and serum potassium concentrations.[25,26]

In addition to the effects of β_2-agonists, patients with asthma or COPD may already be at increased risk of cardiovascular complications. Thus, β_2-agonists must be used with caution in patients with cardiovascular disease because they may precipitate cardiac events.[26]

Tobacco or Drug Abuse

In developed countries, about 25% of both the general population and patients with asthma smoke cigarettes.[27] In patients with asthma, cigarette smoking is associated with worse symptom control, accelerated decline in lung function, and an increase in mortality rate following a near-fatal asthma attack. Further, smokers have impaired response to both short-term inhaled and oral corticosteroids.[27] Patients with asthma who smoke should make a strong effort to quit smoking. Responsiveness to corticosteroids generally improves with smoking cessation.

Although inhaled illicit drug use has been associated with respiratory symptoms, the effect of inhaled illicit drug use on asthma is still under investigation. A study

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of subjects who inhaled heroin mixed with cocaine vaporized on aluminum foil showed that the drug mixture was capable of triggering asthma in healthy subjects, particularly in subjects with a history of childhood asthma.[28] In 62 subjects from a drug rehabilitation center, there was a 41.9% prevalence of wheezing over the past 12 months, a 44.4% prevalence of bronchial hyperreactivity, and a 22.0% prevalence of asthma, defined as wheezing plus bronchial hyperreactivity. Prevalence for wheezing, bronchial hyperreactivity, and asthma in the control population was 32.78% ($P = 0.22$), 15.57% ($P < 0.0001$), and 8.19% ($P < 0.01$), respectively. Of subjects who denied having symptoms prior to use of the drug mixture, 31.4% developed wheezing after beginning the drug.

Obesity

Both obesity and asthma are prevalent disorders. About 65% of US adults over 20 years of age are either overweight or obese.[29] Obese individuals have a greater risk of developing asthma than nonobese individuals, and obesity is associated with worsening of respiratory symptoms and quality of life in people with asthma. Conversely, weight loss improves lung function, symptoms, morbidity, and health status.[30,31] Assuming a 30% prevalence rate of obesity and RR ranging from 1.6 to 3.0, about 15% to 38% of asthma in adults is aggravated by obesity and is thus an important consideration.[31]

The association between obesity and asthma is supported by both animal studies and by epidemiological studies in humans.[30] Adipose tissue increases levels of several proinflammatory molecules, including leptin. Animal studies suggest leptin is associated with enhanced airway inflammatory responses. In humans, large cross-sectional studies show an increased prevalence of asthma in obese adults compared with the general population. Likewise, many studies show an excess of obesity among adults with asthma.[31]

Elucidating the relationship between obesity and asthma is complicated by the fact that obesity causes alterations in pulmonary physiology, which in itself may lead to dyspnea or other respiratory symptoms. Furthermore, decreased physical activity associated with having asthma can lead to obesity, making it difficult to determine cause versus effect.

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Hypertension

Hypertension is prevalent in adult populations, especially in the elderly. Hypertension increases risks of myocardial infarction, heart failure, stroke, and kidney disease. Although antihypertensive medication clearly benefits individuals with hypertension, many elderly patients neglect taking their medication when unrelated chronic medical illnesses are also co-present.[32] In a large-scale study of 51,517 patients 65 years of age or older, anti-hypertensive use was consistently lower in patients who also had asthma or COPD (odds ratio [OR], 0.43; 95% CI, 0.40 to 0.47).[32]

The Expert Panel of the NAEPP guidelines recommends that physicians should review medications for possible exacerbation of asthma. β-Blockers taken for hypertension (particularly nonselective β-blockers) or β-blockers found in some eye drops, may be problematic. Patients should be advised to avoid nonselective β-blockers. Cardioselective β-blockers may be administered to patients with mild to moderate airway obstruction after careful evaluation.[4]

Symptomatic comorbidities such as asthma may seem more pressing to treat than hypertension, which is relatively asymptomatic in nature. Also, patients with more health conditions may have less time and resources available to adequately address each condition.

Depression

The coexistence of depression in individuals with asthma is substantially related to quality of life and to intake of corticosteroids.[33] In a review of the literature on depression and asthma, authors conclude that subjective measures of asthma severity may be more strongly related to depression than objective measures.[34] Specific symptoms, such as dyspnea, wakening at night, and morning symptoms, were particularly strongly associated with depression. Oral corticosteroid use has also been associated with depression.

Depression can produce asthma exacerbations and is negatively associated with asthma treatment compliance and use of corticosteroids.[34]

Arthritis

Inflammatory mechanisms play a role in both rheumatoid arthritis and in airway inflammation and hyperresponsiveness in individuals with allergic asthma. Drugs targeting inflammatory substances in arthritis may also help treat asthma. Tumor necrosis factor-alpha (TNF-α) plays a role in many chronic inflammatory diseases, including rheumatoid arthritis. Elevated levels of TNF-α are frequently observed in bronchoalveolar fluid of asthmatic subjects undergoing allergen challenge, and TNF-α exposure increases airway responsiveness in both normal subjects and subjects with asthma. Thus, drugs developed to neutralize the harmful effects of TNF-α may also be useful in the management of chronic severe asthma.[35]

Sauleda et al[36] measured the activity of cytochrome oxidase in patients with stable COPD, bronchial asthma, chronic arthritis, and in healthy controls. Cytochrome oxidase is the terminal enzyme of the mitochondrial electron respiratory chain and may be affected by several inflammatory mediators, such as reactive oxygen species and cytokines. Compared with healthy subjects, patients with COPD showed increased cytochrome oxidase activity that was negatively related to degree of airflow obstruction ($r = -0.53$; $P < 0.05$). Activity of cytochrome oxidase was also higher than normal in patients with chronic arthritis ($P < 0.05$) and in patients with bronchial asthma ($P < 0.001$). These studies indicate that a similar chronic inflammatory state exists in both rheumatoid arthritis and in allergic asthma.

Stroke

Some evidence suggests that pulmonary inflammation is linked to stroke. In a study combining databases for weather, air pollution, and counts of airborne allergens, a higher incidence of stroke was associated with higher air temperature, dry air, upper respiratory infection, grass pollen, sulfur dioxide, and suspended particles, factors that are also associated with increased risk of asthma.[37]

Osteoporosis

Osteoporosis is associated with vertebral and hip fractures and occurs more frequently in women than men. The prevalence and severity of osteoporosis increase with age. Patients with asthma and COPD are at increased risk for osteoporosis, especially patients treated with corticosteroids for long periods of time.[38] Studies suggest that in addition to systemic corticosteroids, high doses of inhaled corticosteroids (ICSs) could possibly also affect bone mineral density.[38] Asthma treatment with triamcinolone acetonide was associated with a dose-related decline in bone density in premenopausal women suggesting certain subpopulations of patients with asthma are at higher risk.[39]

In addition to medications, other factors may increase risk of osteoporosis in individuals with asthma. The immobility associated with moderate to severe asthma is associated with reduced weight-bearing exercise, decreased muscle mass and strength, and decreased sun exposure, reducing amounts of vitamin D in the body. Also, smoking, a contributor to asthma for many individuals, decreases calcium from the gastrointestinal tract, lowers estrogen levels, and increases bone resorption.[38]

Allergic Bronchopulmonary Aspergillosis

Aspergillus is a genus of mold that is found worldwide. Sensitization to *Aspergillus* increases the severity of asthma and is associated with hypersensitivity respiratory disorders, including allergic bronchopulmonary aspergillosis (ABPA).[40] In a prospective study of 105 subjects with asthma, 30 patients (28.5%) had a positive skin reaction to *Aspergillus* antigens, 10.4% had positive specific reactions to immunoglobulin G, and 7.6% had positive serum precipitins. None of the control subjects were sensitized to *Aspergillus*. Patients with *Aspergillus*-sensitive asthma and ABPA had a more severe form of the disease. These results suggest individuals with asthma should be screened for sensitization to *Aspergillus* to identify individuals at risk.

Pregnancy

Asthmatic women also have increased risk of complications during pregnancy and require close follow-up and adjustment of medications. Pregnancy affects asthma control differently in different women, with asthma control worsening in about one third of pregnant women with asthma, improving in one third of women, and remaining unchanged in one third of women.[41]

Effects of both the illness and the treatment on the developing fetus must be considered. Pregnancy out-

comes for women with well-managed asthma are similar to outcomes of women without asthma. Most drugs used to treat asthma are not associated with increased risk of fetal abnormalities. Inhaled steroids have been shown to prevent exacerbations of asthma in pregnancy, which can cause fetal hypoxia. A meta-analysis of studies that investigated birth outcomes following exposure to ICSs during pregnancy showed that ICSs do not increase risk for fetal malformations, preterm delivery, low birth weight, or pregnancy-induced hypertension.[42] However, oral corticosteroid use during the first trimester has been associated with a 0.3% risk for isolated cleft lip while the risk in the general population is 0.1%.[43] For pregnant women with asthma, poor control usually poses a greater risk to mother and fetus than medications.[2]

KEY POINT

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PREVENTION OF ASTHMA EXACERBATIONS IN ESTABLISHED PATIENTS

Identifying factors associated with asthma exacerbations and reducing exacerbations associated with intensive health care use, such as asthma-related emergency department visits or hospitalizations, will make better use of health care resources and reduce the socioeconomic burden of asthma.

Recent severe asthma exacerbations are a strong independent predictor of future exacerbations and should be considered in the clinical assessment and treatment of patients with severe asthma. In a 1.5-year study of 2780 patients ages 12 years and older, patients with a recent exacerbation were at increased risk for future exacerbations (OR = 6.33; 95% CI, 4.57 to 8.76), even after adjusting for demographics, clinical factors, and asthma severity.[44] Results suggest that recent exacerbations are not adequately represented in asthma severity classifications, and that asthma control better reflects risk of future asthma exacerbations than measures of asthma severity.

A rigorous and systematic approach is needed for diagnosing and treating patients with asthma that is difficult to control.[44] Diagnostic approaches are geared toward determining if asthma is the correct diagnosis. Next, triggers that worsen asthma are identified and eliminated.

Most patients with asthma that is difficult to control will need treatment with high-dose ICSs and long-acting inhaled β_2-agonists.[45] They may also require frequent bursts or even daily therapy with oral corticosteroids. Long-term treatment with higher doses of ICSs, however, may allow decrease or withdrawal of oral corticosteroids. ICSs have minimal systemic effects when taken at recommended doses and should be routinely prescribed as first-line therapy in adults with persistent asthma.[46] Omalizumab may be considered for patients who have allergies, severe asthma, and who need to be on intense ICS therapy.

ICSs are the most effective controller medications currently available to prevent asthma exacerbations and are recommended as the most effective long-term therapy available for patients who have persistent asthma by the NHLBI.[2,4] As shown in the **figure**, corticosteroids have beneficial effects on both inflammatory and structural cells in patients with asthma.[45,47] Corticosteroids improve lung function and decrease airway hyperresponsiveness, reducing symptoms and the frequency and severity of exacerbations, ultimately improving quality of life.[2]

OBSTACLES TO MEDICATION ADHERENCE IN ADULT PATIENTS

Improved adherence to ICS regimens would reduce morbidity, mortality, and use of health care resources. Studies have shown that adherence to single inhaler regimens is better compared with adherence to separate inhaler regimens.[48] Patient perceptions of the risk: benefit ratio and copay issues also affect patient adherence. In a study by Stempel et al,[48] a total of 3503 subjects were identified based on their medication (fluticasone/salmeterol in a single inhaler ([996]), fluticasone and salmeterol in separate inhalers ([259]), fluticasone and montelukast ([101]), fluticasone alone ([1254]), and montelukast alone ([893]). Results showed that adherence profiles of fluticasone and salmeterol in a single inhaler were significantly better when compared with the controller regimens of fluticasone and salmeterol in separate inhalers. The results of this study suggest that patients may be motivated to adhere to regimens that are perceived as simpler with fewer individual medications.

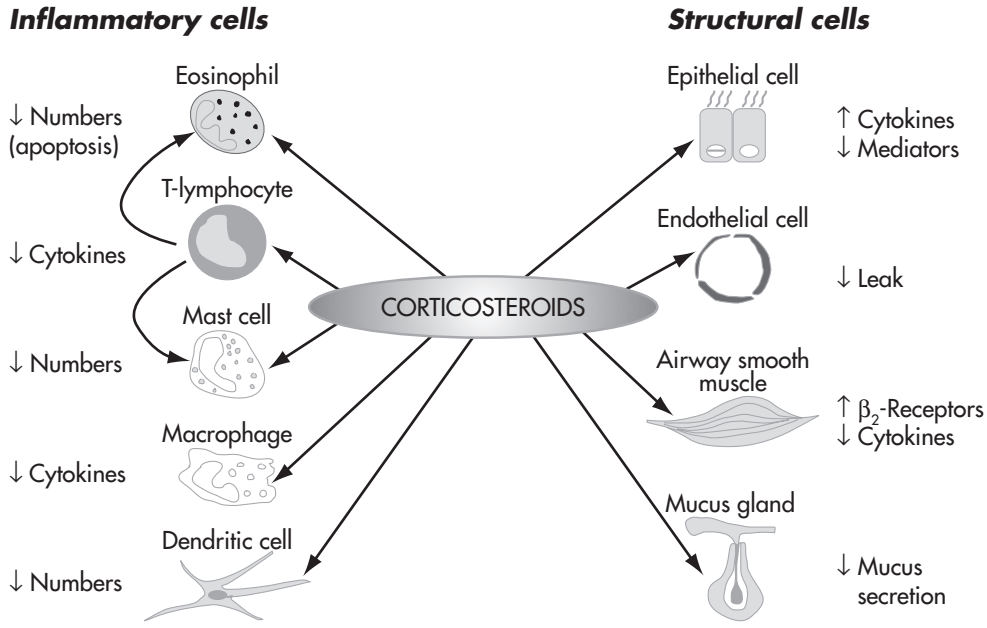

Figure. Effects of corticosteroids on inflammatory and structural cells in asthma. Reprinted with permission.[47]

BENEFITS OF WRITTEN ACTION PLANS

Guided self-management of asthma allows individuals to make changes in treatment, in response to changes in the severity of asthma, according to predetermined guidelines.[2] Written action plans are an important part of guided self-management and can increase medication adherence, reducing morbidity and mortality, conserving health care resources, and improving quality of life.

In a Cochrane review of 25 studies of adults with asthma comparing asthma self-management education interventions to medical care without education, inclusion of written action plans in addition to education had the greatest benefits.[49] Use of written action plans in these studies was associated with reduced emergency department visits and hospitalizations and improved lung function. The Expert Panel of the NHLBI recommends that clinicians provide patients with written asthma action plans that include instruction of (1) daily management and (2) recognizing and handling worsening asthma as part of the overall effort to educate patients in self-management of asthma.[4]

CONCLUSIONS

Chronic asthma is common worldwide and exerts a substantial socioeconomic burden on individuals and on society. Asthma is more accurately thought of as multiple overlapping syndromes rather than a single disease entity. Advances in adult asthma in recent years involve innovations in lung imaging, including the development of imaging sensitive to changes in bronchioles, and use of written asthma action plans. Accurate diagnosis of the cause of chronic cough in adults and of asthma in elderly individuals will help affected individuals receive appropriate treatment. Adults with asthma tend to have higher rates of selected comorbidities, each of which is associated with special treatment considerations. ICSs are the recommended first-line therapy for persistent asthma and can help prevent exacerbations in patients with asthma that is not well controlled. Finally, written asthma action plans may enhance adherence with treatment regimens, ultimately improving quality of life and making the best use of limited health care dollars.

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Dialogue Box

EDITORIAL BOARD

You indicated that asthma represents multiple overlapping syndromes. Does that explain why some patients respond better to specific treatments than others?

GELFAND

What we're saying is that asthma pathogenesis is heterogeneous with respect to the cells and mediators that are responsible for varying in different patients. In fact, even within the same patient at different stages of the disease, the pathways may differ. As a result, we are moving more to the concept of individualizing our treatment approach since it is apparent that one approach doesn't fit all, either between patients or within the same patient. The same may be said for sensitivity to drugs which are likely genetically determined to some extent, as well as the incidence of adverse events.

EDITORIAL BOARD

Are patients with asthma more susceptible to angiotensin-converting enzyme (ACE) inhibitors and the cough associated with them?

GELFAND

The question that arises when somebody comes in with the diagnosis cough-variant asthma is whether they really have asthma or just a drug-induced cough. It is not so much a question of whether asthma predisposes them to the cough induced by an ACE inhibitor. A patient with a history of asthma as a child can be safely prescribed an ACE inhibitor and informed like everybody else about the consequences of taking it, including the possibility of a resultant cough.

EDITORIAL BOARD

In obese asthmatic patients, are there any studies which demonstrate that weight reduction will help their asthma?

GELFAND

That's a great question. It's really the subject of a lot of clinical and basic research and it's not easy to answer. I think for anybody who has a breathing disorder, regardless of the cause, reducing obesity will improve it. But whether treating obesity actually favorably impacts airway hyperresponsiveness per se is not clear. Nevertheless, weight loss will improve obese asthmatic patients' quality of life and likely lung function, and holds the potential for allowing them to require fewer or lower doses of medications.

EDITORIAL BOARD

Are hormones responsible for the gender difference in asthma prevalence?

GELFAND

There have been a number of studies that have looked at this and there's no question that there's a flip in the prevalence around puberty when females are far more likely to have asthma than males. Hormonal influences likely play a role at puberty, at the time of menopause, and possibly when a female subject goes on the pill or is pregnant. In fact, just today I read a paper about menopausal asthmatic women with lower estrogen levels having lower lung function than premenopausal women, regardless of smoking status. Hormones don't likely operate alone—together with genes, environmental factors, and other things, it appears they play a role in controlling airway function.

EDITORIAL BOARD

Can you elaborate on diffusional kurtosis imaging (DKI)?

GELFAND

This diagnostic procedure uses hyperpolarized helium, which permits imaging of particularly distal airways—this offers an advantage over other types of imaging since asthma is a disease not only of central but also of peripheral or distal small airways. The function of distal airways has always been somewhat of a black box for us because when we do lung function tests that measure forced expiratory volume in 1 second (FEV_1), what we're measuring primarily is function in the larger cen-

Dialogue Box

tral airways. DKI gives us a way of examining the distal airways in a noninvasive manner.

EDITORIAL BOARD
Why is this of value?

GELFAND
This is helpful because we know that patients may be very symptomatic despite having a normal FEV_1. Studies like DKI can help direct medication adjustments to impact the distal airways. For example, it is possible that certain types of inhalers (such as inhaled corticosteroids [ICSs]) may offer advantages in terms of small particle distribution and a greater capacity for getting to these peripheral airways. Studies like DKI may also be able to help us determine whether particle distribution is important and whether a change in the type of steroid or the type of inhaler might be of benefit to a particular individual. Such studies are only beginning now.

EDITORIAL BOARD
Does having a peak flow meter in the office suffice or should all physicians invest in office spirometry?

GELFAND
All offices should really offer spirometry. The machines are very easy to use and they're really not that expensive. Most cost under $2000 and it's a reimbursable test. In addition, the software is good and requires very little training; it's terrific for the diagnosis and the monitoring of asthma care. Not surprisingly, the guidelines favor spirometry.

EDITORIAL BOARD
How do you approach the patient with chronic cough?

GELFAND
The main question in such a patient is whether the cough is a manifestation of underlying reactive airway disease or asthma. Cough in children is the most common presenting feature of asthma. In adults, it's a bit more complicated because other etiologies such as bronchitis or smoking may also be the cause. The best way to distinguish asthma is by looking at lung function using spirometry. You can see if there's scalloping in a patient's flow volume loop. In addition, you can give them a bronchodilator and see if it reverses.

EDITORIAL BOARD
In many such patients, the use of short-acting β-agonists doesn't seem to really help.

GELFAND
Right. And that's because they're taking a large amount of a β-agonist or there's something else going on such as smoking or bronchitis. What you never want to use is a long-acting β-agonist alone. Unfortunately, some physicians say, well, instead of using your short-acting inhaler regularly, let's put you on a long-acting β-agonist. As you know, such a practice runs the risk of causing adverse events, including those seen in the Salmeterol Multicenter Asthma Research Trial. Thus, in someone who has a chronic cough, it's imperative to look at lung function and potential reversibility.

EDITORIAL BOARD
Should testing for sputum eosinophils be a routine part of evaluating a patient for asthma?

GELFAND
It's an academic test right now and its diagnostic reliability and clinical utility remain to be validated. Exhaled nitric oxide is another indicator of lower-airway eosinophilia, but this also remains strictly a research tool.

EDITORIAL BOARD
You mentioned a study where 28% of patients with asthma had a positive skin reaction to *Aspergillus* antigen. Does this equate to their having allergic bronchopulmonary aspergillosis (ABPA)?

GELFAND
No, it's just the nature of what's going on. Many of the asthmatics in that study were on steroids and that was

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likely a predisposing factor to such a high percentage of patients demonstrating a positive skin test. A chest x-ray often permits you to distinguish between the two—in the hypersensitivity group, you have central lobular bronchiectasis, whereas in asthma, you have more of secondary plugged airways. The immunoglobulin E (IgE) also tends to be much higher in the patient with hypersensitivity pneumonitis with specific IgE to *Aspergillus*. The possibility of ABPA should be considered in patients not responding to ICSs since hypersensitivity pneumonitis is not going to respond ICSs.