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ORIGINAL RESEARCH

Asthma and the unified airway

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Inflammatory processes of the upper and lower airway commonly co-exist. Patients with upper respiratory illnesses such as allergic rhinitis and acute and chronic rhinosinusitis often present to both otolaryngologists and primary care physicians for treatment of their symptoms of nasal and sinus disease. These patients often have concurrent lower respiratory illnesses such as asthma that may be contributing to their overall symptoms and quality of life. Unfortunately, asthma frequently remains undiagnosed in this population. It was the objective of this paper to examine the relationship between upper respiratory illnesses such as rhinitis and rhinosinusitis and lower respiratory illnesses such as asthma, and to provide a framework for primary care and specialty physicians to approach these illnesses as a spectrum of inflammatory disease. The present manuscript was developed by a multidisciplinary workgroup sponsored by the American Academy of Otolaryngic Allergy. Health care providers in various specialties contributed to the manuscript through preparation of written materials and through participation in a panel discussion held in August 2006. Each author was tasked with reviewing a specific content area and preparing a written summary for inclusion in this final document. Respiratory inflammation commonly affects both the upper and lower respiratory tracts, often concurrently. Physicians who are treating patients with symptoms of allergic rhinitis and rhinosinusitis must be vigilant to the presence of asthma among these patients. Appropriate diagnostic methods should be used to identify individuals with concurrent respiratory illnesses, and comprehensive treatment should be instituted to reduce symptoms and improve quality of life.

INTRODUCTION

It has become increasingly clear that respiratory inflammation affects both the upper and lower airways. Both epidemiologic and pathophysiologic links have been described among diseases such as allergic rhinitis, chronic rhinosinusitis, and asthma. Because common processes of airway inflammation are seen in these various respiratory illnesses, physicians who frequently diagnose upper airway diseases such as rhinitis and rhinosinusitis encounter patients with asthma on a daily basis. In many of these patients, however, the presence and severity of asthma is unappreciated.

Physicians such as family medicine specialists, internists, and otolaryngologists must be vigilant for the presence of asthma among patients with upper airway complaints. Otolaryngologists and other specialists must

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therefore be aware of the concurrent role of inflammation in the upper and lower respiratory systems. Otolaryngologists, who have not traditionally managed patients with asthma, must become increasingly familiar with the signs and symptoms of asthma, particularly as they interface with upper airway disorders such as allergic rhinitis and acute and chronic rhinosinusitis.[1] Among those physicians who diagnose and treat allergic diseases as a significant component of their practices, knowledge of techniques in the diagnosis and management of asthma can improve patient care and maximize patient outcomes among this population.

It is the purpose of this monograph to examine the close relationship between the upper and lower airways as it impacts the care and treatment of patients with upper respiratory inflammatory illnesses such as allergic rhinitis and rhinosinusitis. This supplement will review epidemiologic and pathophysiologic data that demonstrate the importance of asthma in the population of patients with upper respiratory diseases. It will offer information on the diagnosis of asthma among these individuals and will discuss guidelines-based management of asthma in both the adult and pediatric populations. This monograph is designed to provide useful information for otolaryngologists and other physicians who are involved in the management of patients with upper and lower airway inflammation.

UNIFIED AIRWAY

Over the past several years, there has been an increasing trend to view the upper and lower airways as an integrated system. This model has been referred to as the "unified airway model" and considers the entire respiratory system, from the nose and paranasal sinuses, through the trachea and larynx, to the distal bronchioles as a functional unit. Local and systemic influences can stimulate reactions throughout this system, and pathophysiologic processes set in motion from these influences exert similar effects in both the upper and lower airways. As the severity of this airway disease worsens, patients will become increasingly symptomatic, both from upper airway symptoms related to allergic and nonallergic rhinitis and from lower airway symptoms related to asthma.[2]

In practice, otolaryngologists encounter patients with upper airway symptoms on a daily basis. These patients will present with nasal airway obstruction, sneezing, and rhinorrhea and will be treated in the otolaryngologist's office with oral and topical medications for rhinitis. It is uncommon, however, for otolaryngologists to consider a concurrent diagnosis of asthma in these patients. This lack of routine awareness of the presence of asthma in many patients with rhinitis lessens the effectiveness of therapy for these patients and decreases the otolaryngologist's ability to achieve maximum patient outcome with therapy. In fact, a recent international consensus meeting has pointed out the importance of considering asthma among patients with rhinitis, stating "when considering a diagnosis of rhinitis or asthma, an evaluation of both the upper and lower airways should be made."[3] In order to encourage otolaryngologists and other physicians in the recognition of lower airway disorders, it is important to examine a review of the epidemiology, burden, and comorbidities of asthma and rhinitis.

The Comorbidities of Upper and Lower Airway Diseases

In 1997, Corren[4] reviewed the relationship of rhinitis and asthma. He noted that nasal symptoms are experienced in as many as 78% of patients with asthma and that up to 38% of patients with allergic and nonallergic rhinitis have concurrent asthma. In addition, he reviewed data that suggested that the presence of rhinitis often precedes the development of asthma. Studies by both Guerra et al[5] and Settipane et al[6] have demonstrated a 3-fold increase in asthma over a 20-year period among patients diagnosed with allergic rhinitis when compared with their nonallergic counterparts. In the Guerra et al study, 1655 patients with allergic rhinitis were included and were compared with 2177 subjects without allergic rhinitis. These patients were then followed prospectively over 20 years and examined for the development of asthma. This study demonstrated that patients with allergic rhinitis had, on average, a 3-fold increase in the prevalence of asthma over this period. In addition, patients with high serum IgE levels at the outset of the study had a 5-fold increase in their likelihood of developing asthma. These findings confirm the important comorbidities of allergic rhinitis and asthma and clearly demonstrate that patients with allergic rhinitis not only have a higher concurrent prevalence of asthma, but an increased risk of developing asthma over time.

In addition to the mere presence of allergic rhinitis as a factor in the concurrent expression of asthma symptoms, the severity of nasal symptoms correlates closely with the severity of asthma symptoms expressed among patients with asthma. Among patients with symptoms of severe allergic rhinitis, there is a higher prevalence of asthma symptoms such as nighttime awakenings and loss of work than among rhinitis patients with less severe symptoms.[7] These findings suggest that the likelihood of asthma being present in patients with severe rhinitis is more common than among patients with rhinitis of lesser severity. Asthma should definitely be considered, therefore, among patients with severe symptoms of nasal congestion, rhinorrhea, and nasal itching who present to otolaryngologists.

Additional research has demonstrated that patients with allergic rhinitis have differential likelihoods of developing asthma as a function of the type of antigen to which they are allergic. Linneberg et al[8] examined the relative risk ratios for the development of asthma among patients with known allergic rhinitis. The authors noted that the relative risk of developing asthma among patients with skin-test demonstrated allergy to pollen was 8.2, to animal

dander was 18.9, and to dust mite was 46.5. Dust mite sensitization, therefore, was demonstrated to be a potent risk factor for the development of asthma, with nearly a 50-fold increase in the likelihood of asthma when compared with nonallergic patients. Again, patients with perennial symptoms of allergic rhinitis are at significant increased risk of developing asthma when compared with nonallergic individuals.

Otolaryngologists frequently diagnose and treat patients with nasal and sinus symptoms. One important symptom of which patients frequently complain is nasal congestion or nasal obstruction. These patients are often the most difficult and challenging patients to treat and require comprehensive treatment that often involves both medical and surgical intervention. It has been well demonstrated that asthmatic patients with nasal airway obstruction will have a decline in pulmonary function when their nasal airflow is diminished. Shturman-Ellstein et al[9] in 1978 demonstrated in a classic study that when asthmatic patients underwent exercise with their noses occluded with a nasal clamp, they had a 20% decline in forced expiratory flow when compared with less than 5% reduction among patients allowed to exercise with patent nasal airways.[9] The authors argued that nasal patency was important in the retention of pulmonary function among asthmatic individuals and that nasal occlusion was an important trigger to a decline in pulmonary function and exacerbation of asthmatic symptoms.

Upper and Lower Airway Inflammatory Crosstalk

Additional support for the relationship between the upper and lower airways is found in research that demonstrates inflammatory interaction between the nose and the lungs. In a series of studies by Braunstahl et al,[10-13] it was demonstrated that antigen placed in 1 area of the respiratory tract was able to demonstrate the upregulation of inflammatory mediators in the most distal areas of that respiratory tract. In these studies, antigen was directly placed into either the nose or directly onto the pulmonary mucosa with the use of bronchoscopic installation. Examination of inflammatory mediators such as the adhesion molecules ICAM-1 and VCAM-1 showed that increases in these mediators could be demonstrated in the nose after direct placement into the lung and vice versa. Similar findings were noted in the pulmonary mucosa after antigen was placed directly into the nose. These studies demonstrate that inflammatory mediators can be upregulated throughout the respiratory system by central regulatory processes triggered by stimulation of any component of the respiratory tract.

In another series of studies, patients with allergic rhinitis have been demonstrated to have increased bronchial hyperreactivity, even though they may not at the time have a diagnosis of asthma. Among patients with seasonal allergic rhinitis without asthma, 11% to 32% of these individuals have been noted to have an bronchial hyperresponsiveness as demonstrated by methacholine challenge when tested outside of their allergy season. During the season in which they have demonstrated allergy, this level of bronchial hyperresponsiveness increases, and 48% of these patients are hyperresponsive to challenge during season.[14] In addition, about 50% of patients with perennial allergic rhinitis without asthma demonstrated hyperresponsiveness to bronchial challenge.[4]

In another study,[15] prior stimulation of the nose with antigen using a nasal provocation challenge was demonstrated to increase bronchial hyperresponsiveness to methacholine challenge. After baseline assessment with methacholine challenge, the nose was challenged with direct application of a sensitized antigen to the nasal mucosa. Bronchial hyperresponsiveness was then determined with standard methacholine challenge via nebulized administration. It was shown that within 30 minutes of nasal challenge with allergen, the lungs became more responsive to stimulation with methacholine and required less stimulation to show a significant response. This study further demonstrated the ability of nasal antigen exposure to stimulate direct fall in lung function, which further confirmed the role of allergic rhinitis in the pathogenesis of bronchial hyperreactivity and asthma.

Further confirmation for this relationship with allergic rhinitis and asthma is noted through studies that demonstrate a reduction in the severity of asthma through the treatment of the patient's allergic rhinitis with topical steroids, antihistamines, or both. In 1 study,[16] patients with mild-to-moderate asthma and concurrent allergic rhinitis were treated with intranasal corticosteroid medications, inhaled corticosteroids, or both. Patients treated with nasal steroids, even without the concurrent use of inhaled medications, demonstrated an improvement in pulmonary symptoms over a 12-week period. The authors concluded that "failure to consider treatment of rhinitis as essential to asthma management might impair clinical control of asthma." Similar findings have been noted in other studies as well.[17,18]

THE RELATIONSHIP OF RHINITIS AND ASTHMA

The connection between asthma and rhinitis is not a recent discovery. Significant progress has been made, however, in understanding this relationship, and the implications of the asthma-rhinitis link make it increasingly important. For example, patients with asthma and rhinitis tend to have more severe disease, and their treatment is associated with higher costs.[19,20] In addition, treatment of rhinitis may improve asthma control,[17,21] and early treatment of allergies may prevent the development of asthma.[22-24] In this section, the epidemiologic, pathophysiologic, and clinical relationships between asthma and rhinitis will be more fully explored.

Epidemiologic Links

Asthma and rhinitis appear to be epidemiologically linked. Various epidemiologic studies have demonstrated that al-

lergic rhinitis is a common disorder in the United States. Prevalence rates of allergic rhinitis range from 15% to 40%.[25,26] The variability in the many epidemiologic studies available may be due to sampling variances and differences in case definition, but regardless, allergic rhinitis is a common disorder and is frequently encountered by the practicing otolaryngologist. Similarly, asthma is a prevalent disorder (the epidemiology of asthma is covered in detail in another section of this supplement.).

Asthma affects approximately 7% of the US population.[25,26] Asthma and allergic rhinitis occur together at rates that greatly exceed that which would be expected from the baseline prevalence of each disorder alone. As noted earlier, up to 38% of patients with allergic rhinitis will also have asthma; this suggests that allergic rhinitis is itself a risk factor for the development of asthma.[4] This assertion has been corroborated by multiple studies.[5,27] In the Finnish Twin Cohort Study,[28] over 11,000 subjects were administered questionnaires in 1975, 1981, and 1990. The study found that men who reported "hay fever" in 1975 had a 4-fold increased risk of reporting asthma in 1990. In women, the effect was even more pronounced with a 6-fold increased risk of developing asthma after they reported hay fever in the earlier survey. Looking at this longitudinal data, the authors also noted that rhinitis was nearly always diagnosed before asthma. This trend, where allergic rhinitis precedes the development of asthma, has also been noted by other authors.[5,27] The natural history of rhinitis and asthma are quite variable between individuals, and asthma may sometimes become manifest before rhinitis, but it is now widely accepted that rhinitis is an independent risk factor for the development of asthma.[3,5,29]

There are multiple factors that influence the linkage between asthma and rhinitis. The association of rhinitis and asthma is dependent on the atopic status of the patient, the age of onset of atopy, as well as the severity of symptoms. It should be noted that atopy is not required for this relationship. Perennial nonallergic rhinitis is also an independent risk factor for asthma.[30] Patients with perennial rhinitis are more likely to have incident asthma than those with only seasonal rhinitis symptoms.[31] Subjects who develop atopy at an earlier age may be more likely to develop asthma. So the association of rhinitis and asthma is independent of allergy, but in allergic patients is dependent to some extent on the severity and persistence of rhinitis symptoms.[5] The pathophysiologic explanation for these observations is still a matter of investigation.

In patients with asthma, rhinitis is extremely common; the vast majority of patients with asthma have rhinitis. Multiple studies have shown rhinitis to be present in 50% to 85% of asthmatic subjects, with the differences between studies likely due to the methods of the study. Reliance on patient self-reporting of symptoms may be insensitive, considering that many patients with asthma may be more bothered by their asthma than any rhinitis symptoms that they take for granted.[29] In a study[19] of 1245 asthmatic subjects in Olmstead County, Minnesota, 52% of asthmatic subjects were found by chart review to have allergic rhinitis and 6% had nonallergic rhinitis. This study also showed that yearly medical care charges were 46% higher in those patients with concomitant asthma and rhinitis. The presence of rhinitis may be associated with more severe asthma. In a study[32] of hospital admissions in 2961 children from Norway, even when correcting for severity of asthma, children with allergic rhinitis had a higher risk of hospital readmission and more hospital days per year when compared with asthmatic patients without rhinitis.[32] Similar findings have been noted from the United Kingdom,[20] and increased costs are seen when asthma and rhinitis are concomitant disorders.[19,33] The fact that most asthma patients have rhinitis has therapeutic implications that will be discussed later.

Although the linkage between asthma and rhinitis is now clear, the exact basis for this connection is still being investigated. Rhinitis that leads to nasal obstruction may cause inspiration of unfiltered and unconditioned air, and theoretically could exacerbate any underlying lung disease. There is also a putative nasobronchial reflex wherein nasal irritation provokes bronchoconstriction.[34] Another likely connection that exists between the lung and nose is systemic, with propagation of nasal or bronchial inflammation so that inflammation in one end organ affects another.

The inflammation in rhinitis and asthma are similar. Many pathophysiologic links connect asthma and rhinitis. First, as discussed earlier, the nasal and bronchial mucosa are histologically similar; inflammation in allergic rhinitis is also similar to that seen in the bronchial mucosa of subjects with asthma. There are differences, of course; nasal obstruction from rhinitis is largely due to engorged capacitance vessels in the nose that lead to turbinate swelling, whereas in asthma, epithelial disruption, basement membrane thickening, and smooth muscle hypertrophy are pathologic developments.[29] The inflammatory cell infiltrate of mononuclear cells, lymphocytes, and eosinophils in both diseases, however, demonstrates marked pathologic similarity, and the cytokines and other important inflammatory mediators are much the same in both diseases.[35-37] In addition, the same triggers, whether viral, irritant, or allergen can trigger both rhinitis and asthma. These common features suggest that asthma and rhinitis are intimately linked disorders.

Rhinitis patients are prone to bronchial hyperreactivity. Patients with rhinitis but without a clinical diagnosis of asthma may be predisposed to the development of bronchospasm or have evidence of hyperreactivity to bronchoconstricting agents on challenge testing. In a population-based study[38] from Europe, the European Community Respiratory Health Survey, odds ratios (OR) demonstrated that self-reported "nasal allergies" were an independent predictor of bronchial hyperreactivity (OR, 1.9 to 6.1). Similarly, even absent any rhinitis complaints, positive allergy skin tests were an independent predictor of bronchial hyperreactivity (OR, 2.2 to

6.7). Different allergen sensitivities may determine the degree of hyperreactivity. In a study[26] that compared allergic rhinitis patients with pollen or dust mite allergy but no clinical diagnosis of asthma, the patients with dust mite allergy had lower methacholine threshold values on bronchial provocation testing, which indicated a greater degree of bronchial hyperreactivity. The finding that rhinitis patients without an asthma diagnosis or asthma symptoms have bronchial reactivity suggests that asthma and rhinitis may be different manifestations of a single respiratory system disease.

The nasal and pulmonary compartments are immunopathologically linked via the bloodstream. The pathophysiologic link between asthma and allergic rhinitis has been elegantly demonstrated by studies from Braunstahl et al[10-12] In 1 study,[11] 9 subjects with grass pollen allergy, but no asthma, were compared with 9 nonallergic subjects. Both groups underwent nasal provocation with grass pollen antigen, and in both groups bronchial and nasal mucosa biopsies were obtained at baseline and at 24 hours postexposure. In addition, nasal and pulmonary symptom scores were obtained with a visual analog scale and peak nasal inspiratory flow and peak expiratory flow (a measure of pulmonary obstruction). The findings from this study were that in allergic patients, but not in controls, nasal provocation stimulated eosinophilia in the bronchial mucosa and resulted in elevated expression of important cell adhesion molecules (ICAM-1, VCAM-1, and E-selectin). In addition to these histologic changes noted in the lungs after challenging the nose, decreases in peak expiratory flow were noted in the first 24 hours, and pulmonary symptoms were noted by subjects in the first few hours after nasal provocation. In another study[10] with a similar design, segmental bronchial provocation with allergen caused an increase in IL-5, eotaxin, and eosinophils in both unchallenged bronchial mucosa and the nasal mucosa. Taken together these studies demonstrate the connection between bronchial and nasal inflammation, and that the inflammation at 1 site provokes inflammation at another site, probably through the hematogenous dissemination of inflammatory mediators and cells.

Treatment of rhinitis impacts asthma outcomes. Just as nasal provocation may trigger pulmonary inflammation and symptoms, treatment of nasal disease can improve parameters in asthma. This phenomenon has been demonstrated in multiple studies,[16,17,39] but was not confirmed in other trials.[40,41] In 1 example, Watson et al,[17] in a double-blind, placebo-controlled crossover trial, showed that intranasal beclomethasone can improve asthma symptoms and reduce bronchial hyperreactivity. In another randomized, double-blind study, Stelmach et al[16] showed that intranasal beclomethasone controlled asthma symptoms as well as inhaled and combination intranasal-inhaled applications of the drug. Combined use of intranasal and inhaled beclomethasone reduced emergency department visits, lost work days, and sleep problems. The profound implication of these studies is that asthma control can be improved by treating rhinitis.

Antigen-specific immunotherapy can prevent asthma in rhinitis patients. Another important clinical relationship is the potential that treatment of rhinitis with immunotherapy can prevent the development of asthma. As noted previously, allergic rhinitis frequently becomes manifest before the development of asthma. Given the significant morbidity and mortality of asthma, any intervention that may prevent its development should be seriously considered. The potential of antigen-specific immunotherapy to prevent the subsequent development of asthma was described as early as 1968.[23] Subsequent work has further supported this concept.[24] The most convincing data come from a prospective multicenter study[22] from Europe. Two hundred and five children with allergic rhinoconjunctivitis to grass and/or birch pollen were randomized to either a specific immunotherapy or an open control group and followed prospectively over 4 years. Immunotherapy was continued for 3 years. During the study period, bronchial hyperreactivity declined in the immunotherapy group. In addition, children without asthma at the start of the study (N = 151) were evaluated for the development of asthma at the end of the 3-year treatment period. At 3 years, 29 (42%) of 69 patients in the control group developed asthma versus 19 (24%) of 79 in the immunotherapy group. Further investigation is needed to confirm the role of antigen-specific immunotherapy in the development of asthma, but the potential to intervene early in the course of disease to alter outcomes is promising.

Rhinitis and Asthma: Summary

The association between asthma and rhinitis should be recognized by otolaryngologists and may impact treatment. Rhinitis patients are at increased risk for the development of asthma or may have unrecognized asthma. An attentive evaluation may uncover a previously unrecognized condition and lead to early intervention, which in turn can improve patient outcomes. About one third of rhinitis patients will have asthma, and most asthma patients have rhinitis. It is likely that asthma and rhinitis are different manifestations of a single respiratory system disease. Treating rhinitis may improve the control of asthma, and thus decrease the cost, morbidity, and potential mortality of this condition.

THE RELATIONSHIP OF RHINOSINUSITIS AND ASTHMA

In recent years, there has been a dramatic increase in clinical interest and research on rhinosinusitis. In 1996, a Task Force on Rhinosinusitis was convened by the Sinus and Allergy Health Partnership and included members of the American Academy of Otolaryngology-Head and Neck Sur-

Table 1
Factors associated with diagnosis of rhinosinusitis (1996 Task Force)

Factors associated with diagnosis of rhinosinusitis	
Major factors	Minor factors
Facial pain/pressure*	Headache
Nasal obstruction/blockage	Fever (all nonacute)
Nasal discharge/purulence/discolored postnasal drainage	Halitosis
Hyposmia/anosmia	Dental pain
Purulence in nasal cavity on exam	Cough
Fever (acute rhinosinusitis only)†	Ear pain/pressure/fullness

Strong history of rhinosinusitis is suggested by 2 or more major factors or 1 major and 2 minor factors. Suggestive history of rhinosinusitis is associated by the presence of 1 major or 2 or more minor factors.
Reproduced from Lanza DC, Kennedy DW. Adult Rhinosinusitis Defined. Otolaryngol Head Neck Surg 1997;117:S1–7.

*Facial pressure alone does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.
†Fever in acute sinusitis alone does not constitute a strongly suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.

gery, American Academy of Otolaryngic Allergy, and American Rhinologic Society. Guidelines for the definition of rhinosinusitis based on symptoms was published in 1997, Adult Rhinosinusitis Defined.[41] These guidelines include major and minor symptom categories as listed in Table 1. In 2002, the Task Force for Defining Adult Chronic Rhinosinusitis extended the recommendations to include duration of symptoms, physical findings, and radiographic imaging as outlined in Table 2.[42] A 2004 multi-disciplinary task force[43] described chronic rhinosinusitis (CRS) as accompanied by 4 common symptoms: purulent rhinorrhea, facial pain/pressure, nasal congestion, and decreased sense of smell. CRS is now recognized as a spectrum of disease and is defined as ". . . a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration."[42]

Table 2
Measures to diagnose CRS for adult clinical care

1. Duration of disease is qualified by continuous symptoms for >12 consecutive weeks or >12 weeks of physical findings*
2. One of these signs of inflammation must be present and identified in association with ongoing symptoms consistent with CRS:
   a. Discolored nasal drainage arising from the nasal passages, nasal polyps, or polypoid swelling as identified on physical examination with anterior rhinoscopy or nasal endoscopy. Anterior rhinoscopy should be performed in the decongested state.
   b. Edema or erythema of the middle meatus or ethmoid bulla as identified by nasal endoscopy
   c. Generalized or localized erythema, edema, or granulation tissue. If it does not involve the middle meatus or ethmoid bulla, radiologic imaging is required to confirm a diagnosis.†
   d. Imaging modalities to confirm the diagnosis:
      i. CT scan: to demonstrate isolated or diffuse mucosal thickening, bone changes, air-fluid level
      ii. Plain sinus radiograph: Water's view revealing mucous membrane thickening of >5 mm or complete opacification of one or more sinuses. An air-fluid level is more predictive of acute rhinosinusitis, but may also be seen in chronic rhinosinusitis.‡
      iii. MRI is not recommended as an alternative to CT for routine diagnosis of CRS because of its excessively high sensitivity and lack of specificity.

Reproduced from Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology and pathophysiology. Otolaryngol Head Neck Surg 2003;129(3 Suppl):S1–32.

*Signs consistent with CRS will support the symptom time duration.
†Other chronic rhinologic conditions such as allergic rhinitis can have such findings, and therefore they may not be associated with rhinosinusitis. It is recommended that a diagnosis of rhinosinusitis require radiologic confirmation under these circumstances.
‡A plain sinus x-ray without the equivocal signs listed in a, b, or c is not considered diagnostic. Aside from an air-fluid level, plain sinus radiographs have low sensitivity and specificity.

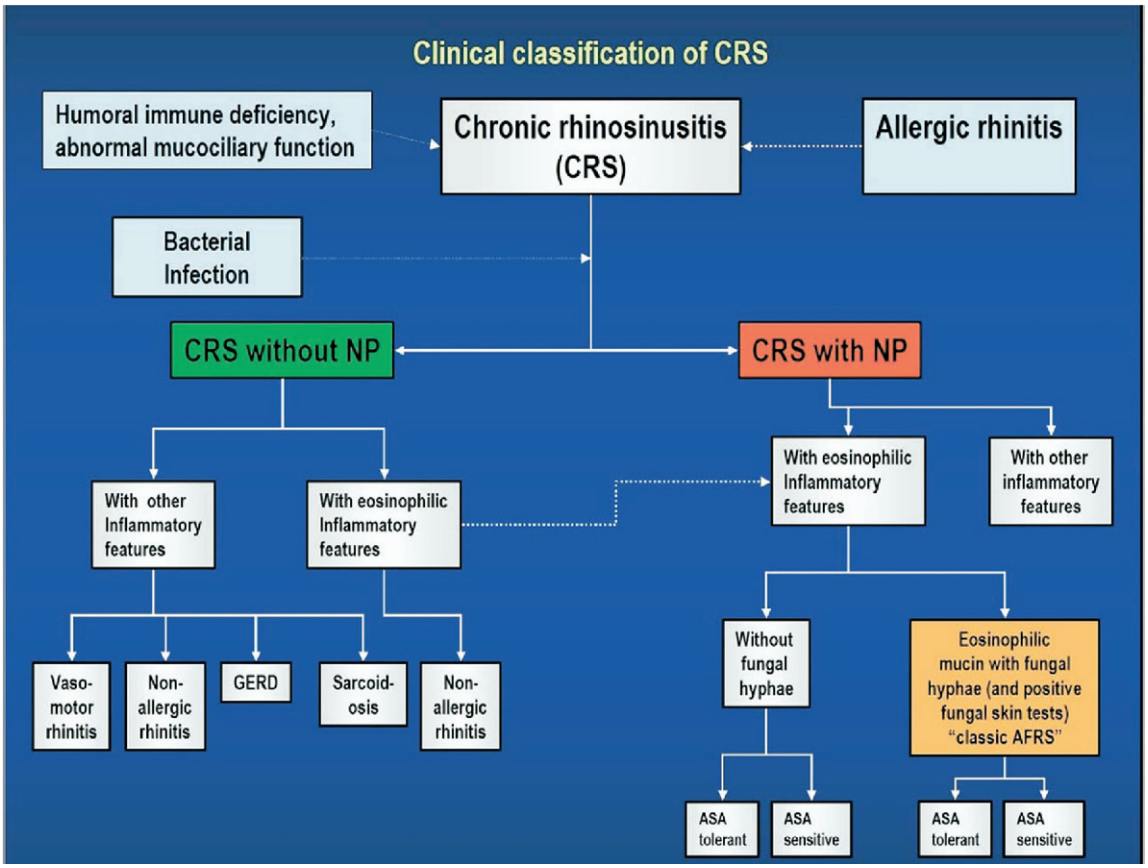

Figure 1 Proposed subclassifications of chronic rhinosinusitis. (Reproduced from: Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. Otolaryngol Head Neck Surg 2004;131:S1–62.)

Rhinosinusitis affects 31 million U.S. patients each year with increasing prevalence and incidence.[43] There are significant effects on quality of life and impact on daily functioning. CRS is responsible for 18 to 22 million physicians' office visits per year in the United States.[42] Trends in office visits and antibiotic prescriptions for sinusitis are increasing. With $200 million spent in 1992, there has been an increasing use of prescription cold medicines with $2 billion spent annually for over-the-counter nasal and sinus medications.[42] Indirect costs are related to the time and resources spent going to the doctor, in obtaining medications, and lost time from work and school. The diagnosis of chronic rhinosinusitis resulted in direct heath care costs of $3.39 billion in the United States with total direct and indirect costs of $5.8 billion in 1996.

Causative factors in rhinosinusitis may vary from infectious causes (microorganisms, bacterial antigens, biofilms, and osteitis) to noninfectious causes (allergic and immunologic inflammation, noninflammatory changes related to trigeminal dysfunction and cholinergic rhinitis, and aspirin-exacerbated respiratory disease).[43] Rhinosinusitis can also be described by extrinsic factors (infectious and noninfectious inflammatory) and intrinsic factors (genetic, autonomic dysregulation, hormonal, autoimmune). Unfortunately, rhinosinusitis is difficult to classify as many of these conditions occur in overlap, and these problems often do not exist in isolation.[43]

One proposed classification scheme is illustrated in Figure 1.[43] For descriptive purposes, rhinosinusitis can be separated based on inflammatory status–eosinophilic vs neutrophilic.[42] The eosinophilic classification more specifically deals with chronic rhinosinusitis with polyps (CRSwNP), a subset of chronic rhinosinusitis without polyps (CRSsNP), aspirin-exacerbated respiratory disease, and allergic fungal rhinosinusitis. It is eosinophilic rhinosinusitis that has the most well-delineated relationship with asthma.

Eosinophilic-mediated inflammation is the key component that perpetuates the disease state in many forms of chronic rhinosinusitis.[42-45] Allergies and atopy may or may not be found with eosinophilic chronic rhinosinusitis. In fact, the level of eosinophilia is equal in both allergic and nonallergic chronic hyperplastic sinusitis with polyps (CHS/NP).[44-46] One half to two thirds of patients with CHS/NP are nonallergic.[45] Among those patients with CRSwNP (in this article, also known as CHP/NP), at least 50% have asthma and 30% to 40% have associated aspirin intolerance.[43,45]

Studies of healthy and chronically inflamed nasal and sinus cavities reveal contrasting cell contents. Lavage of healthy nasal cavities shows 50% to 60% epithelial cells,

35% to 40% neutrophils, and less than 5% eosinophils.[47] Puncture and lavage of the normal sinus maxillary sinus shows 63% epithelial cells, 28% neutrophils, 9% monocytes, and less than 1% eosinophils and mast cells. In contrast, lavage and sinus mucosal biopsy in chronic rhinosinusitis shows a greater number of eosinophils localized and found aggregated within and beneath the epithelium. Mast cells and lymphocytes are also seen. Neutrophils are seen in much fewer numbers.[46,48]

Eosinophil chemotaxis and activation in chronic rhinosinusitis occur via a variety of mechanisms. Interleukin-5 (IL-5) produced by T-lymphocytes promotes eosinophil activation and prevents eosinophil apoptosis. The locally produced cytokine, GM-CSF (granulocyte macrophage colony-stimulating factor), is also found to promote eosinophil activation and survival. Local production of the chemokines, RANTES (regulated upon activation, normal T-cell expressed, and presumably secreted) and eotaxin, assist with the transendothelial migration of eosinophils and their movement into the epithelium. The expression of vascular cell adhesion molecule (VCAM-1) on endothelial cells mediates selective transendothelial migration of eosinophils and lymphocytes.[44,45,48] The abundant infiltration of eosinophils and inflammatory mediators is linked with the inflammation found in both CRSwNP and the associated subset of CRSsNP.

Interestingly, the eosinophilic category of CRS is strongly associated with asthma both clinically and pathologically.[43] The nonallergic eosinophilic inflammation seen in the upper airway is pathologically quite similar to that seen in the lower airways.[44] For the upper airway, this has been studied in chronic hyperplastic sinusitis with nasal polyps (CHS/NP or CRSwNP) and for the lower airway this has been described as intrinsic or nonallergic asthma.

For over 70 years, there has been a recognized coexistence and suspected association between asthma and sinusitis.[48-50] "Asthma and rhinosinusitis coexist at a higher frequency than would be expected from the prevalence of each alone in the general population."[44] The prevalence of asthma in the general population is 5% to 8%. On the other hand, patients with chronic rhinosinusitis have a 20% prevalence of asthma.[44] This coexistence is seen in greater numbers of patients who undergo functional endoscopic sinus surgery with a 42% prevalence rate.[51] Twenty percent of all patients with chronic rhinosinusitis have polyps. Among these patients, the prevalence of asthma is 50%.

Table 3
Common histopathologic findings in CRS and asthma

Eosinophilic infiltration
Lymphocyte infiltration
Major basic protein deposition
Basement membrane thickening
Goblet cell hyperplasia
Mucus hypersecretion
Subepithelial edema
Epithelial damage
Submucosal gland formation

Table 4
Common inflammatory mediators and cells in CRS and asthma

Eosinophils
IL-5 producing lymphocytes
Inflammatory mediators:
Cytokines IL-4, IL-5, and IL-13
Cysteinyl leukotrienes:
Chemokines
RANTES
Eotaxin
Endothelial adhesion proteins, ICAM-1 and VCAM-1

The respiratory lining of the nose, paranasal sinuses, and primary and secondary bronchi is composed of pseudostratified, ciliated, columnar epithelium. As such, it would follow that chronic inflammation of the airway would involve similar cells and pathoses. The histopathologic findings in asthma show basement membrane thickening, goblet cell hyperplasia, subepithelial edema, submucosal gland formation, polymorphonuclear (PMNs) leukocyte cell infiltration, and mucus hypersecretion. These common findings are summarized in Table 3. These findings of airway remodeling are signs of chronic inflammation and are the same histopathologic changes described in chronic rhinosinusitis.[48,52-55] These histopathologic findings are worse when rhinosinusitis and asthma are seen together when compared with the pathoses that are seen in each condition separately.[52]

Histopathologic studies also confirm that the effector cell associated with chronic inflammation in both CRS and asthma is the eosinophil. The eosinophil is found in the nose in asthmatic patients with or without nasal symptoms. Extensive eosinophil infiltration is seen in patients with both chronic rhinosinusitis and asthma and/or allergic rhinitis; this is less apparent in cases of chronic rhinosinusitis alone.[53]

More specifically, there are striking similarities seen in chronic eosinophilic inflammation involved in nonallergic CRSwNP when compared with intrinsic asthma. This suggests that a similar pathologic process is involved in both conditions.[44] These common mediators are summarized in Table 4. Lemanske and Busse[56] found that the inflammation in asthma involves activated mast cells with cytokines recruiting and activating eosinophils. Lymphocytes are also found; particularly T-helper 2 lymphocytes–those seen in allergy and that release cytokines IL-4, IL-5, and IL-13. Lymphocytes and epithelial cells generate the chemokines, RANTES and eostaxin, both essential for eosinophil recruitment as mentioned earlier. The activation of endothelial adhesion proteins, ICAM-1 and VCAM-1, leads them to combine with receptor sites on inflammatory cells. This reduces the flow of the inflammatory cells in blood vessels and assists with their transmigration to airway. This inflammatory cascade leads to airway edema and narrowing

through increased capillary membrane permeability and triggering of airway smooth muscle spasm.[56]

These similarities between CRS and asthma support the idea of "united airway disease" or "one airway disease," discussed earlier. In addition to studies that link the histopathology of CRS and asthma, investigators have attempted to determine how the upper airway impacts the lower airway. The concept of systemic amplification via systemic interaction is one explanation for this idea. This "ability of one airway compartment to impact disease in another (remote) airway compartment" does seem to occur at the cellular level with involvement by eosinophils, T-lymphocytes, and their inflammatory mediators.[44] One suggested mechanism for this amplification is signaling through the bone marrow with release of inflammatory progenitors, such as eosinophil-basophil progenitors, into the peripheral blood and for recruitment to the upper and lower airways. Through their research, Jani and Hamilos[44] and Denburg[57] have shown that the airway has the capacity to produce hematopoietic growth factors that drive the maturation of such inflammatory cell progenitors.

Consideration that CRS and asthma are part of a systemic inflammatory disease process fits well with clinical observations of shared pathogenesis. Clinical studies have confirmed connections between asthma and chronic rhinosinusitis. Harlin et al[53] in 1988 hypothesized that the eosinophil participates in the pathogenesis of chronic rhinosinusitis in patients with asthma. They studied 4 patient groups: 1) chronic rhinosinusitis alone, 2) chronic rhinosinusitis and allergic rhinitis, 3) chronic rhinosinusitis and asthma, and 4) chronic rhinosinusitis, asthma, and allergies. Specimens from Caldwell-Luc, intranasal ethmoidectomy, and transnasal ethmoidectomy procedures were examined histologically by hematoxylin and eosin staining, examined for the degree of eosinophilia, and immunofluorescent localization for the presence of the eosinophil granule, major basic protein (MBP). The results revealed marked basement membrane thickening in patients with chronic sinusitis (CS) and asthma; greater than that seen in CS without asthma. There was significant extracellular deposition of MBP in sinus tissue that was seen only when asthma was present. The authors concluded that this is histopathologic confirmation that changes seen in sinusitis are similar to that seen in asthma.

Two notable studies have used the extent of sinus disease as determined by computed tomography (CT) to evaluate for an association between sinusitis and severe asthma. Bresciani et al[58] compared 2 patient groups with sinusitis: 35 patients with severe steroid-dependent asthma, and a group of 34 patients with mild to moderate asthma. Sinonasal involvement was measured by clinical symptom scores and the extent of disease as seen on CT. The frequency of rhinosinusitis was similar in both groups, but sinonasal involvement was significantly greater in the severely asthmatic patients. In another study, ten Brinke et al[59] investigated whether the extent of nasal mucosal inflammation was related to the inflammation seen in asthma and poor lung function in severe asthmatics. Eighty-nine severe asthmatics were evaluated by several measures: sinus CT scan scores, lung function, blood and sputum eosinophilia, and nitrous oxide in exhaled air. Eight-four percent of the patients had abnormal sinus CT scans. Significant correlations were found between CT scan scores and eosinophil counts, levels of exhaled nitric oxide, and lung function (functional residual capacity and diffusion capacity). They concluded that there was a direct correlation between sinonasal mucosal thickness and bronchial inflammation in severe asthma that indicated an association between upper and lower airway inflammation.

The results of the above studies and others suggest that the improvement of asthma after the treatment of CRS is a result of reduced bronchial inflammation. Improvement of the asthmatic condition has been shown in several studies that looked at the effect of surgery for rhinosinusitis. Outcomes measures have included symptom scores, pulmonary function tests, the type of surgery performed, and changes in symptoms associated with CRS and asthma.[60-63] Overall, the treatment of CRS with surgery and postoperative care is associated with improvement in asthma and decreased asthma medication use, particularly the use of inhaled and systemic steroids. Furthermore, continued medical therapy of sinusitis postoperatively has been associated with continued asthma control with demonstrated long-term improvement that ranged from 6 months to 6 years. Unfortunately, the studies done to date are uncontrolled for the effect of the treatment intervention. There are also no randomized controlled studies that look at the effect of medical therapy of sinusitis on concomitant asthma.

The finding that the treatment of rhinosinusitis positively affects asthma control again supports the idea of systemic amplification–a systemic interaction involved with the inflammatory response. This interaction has been shown in other ways as well. For example, proinflammatory mediators and cytokines released during rhinitis act to also exert an effect on the lower airway.[44,48] Thus, control of rhinosinusitis potentially leads to a reduction of systemic inflammatory signals. This is supported by the benefits of intranasal steroids in the upper airways that are associated with decreased bronchial hyperresponsiveness.[44,64] In a commonly referenced study[65] on pediatric patients, antibiotic treatment of rhinosinusitis showed improvement in asthma symptoms, decreased bronchodilator use, and improvement in pulmonary function tests. Other proposed mechanisms for a connection between CRS and asthma include: 1) nasobronchial and/or pharyngobronchial reflexes via neural mediation with resultant bronchoconstriction, and 2) influence of eosinophilic inflammation by *Staphylococcus aureus*-derived enterotoxins (SAEs).[44,48] In this latter case, it is speculated that nasal droplets that contain SAEs are inhaled into the lower airway.

The triad of aspirin sensitivity, asthma, and sinonasal polyps was first described by Widal in 1922.[66] Later studies

were done separately by Samter and Beers.[66] The clinical presentation begins with rhinorrhea and nasal congestion and reports of cold symptoms. This rhinitis is usually first seen in the patient's fourth decade. Rhinitis becomes persistent and recurrent sinusitis develops. This then progresses to persistent rhinosinusitis with the eventual development of sinonasal polyps. Asthma and aspirin sensitivity may manifest as much as 1 to 5 years after the onset of the first symptoms.[66,67] Unfortunately, the disease state progresses whether or not the patient ingests cyclo-oxygenaxe 1 inhibitors.[43]

The incidence of aspirin sensitivity in the general population is 0.6% to 2.5% and 5% to 10% in adults with asthma.[56,66] Fifty percent of the patients with aspirin sensitivity have chronic severe corticosteroid-dependent asthma, 30% have moderate asthma, and 20% have mild or intermittent forms of lower airway disease. Seventy percent of aspirin sensitive patients have sinonasal polyps.[66,67] The ingestion of aspirin leads to an acute asthma attack within hours that may be potentially life-threatening. This episode is accompanied by profuse rhinorrhea, orbital edema, conjunctival infection, and flushing of the head and neck.[66,67]

The exact mechanism of aspirin intolerance is unclear. The aspirin sensitivity seen in Samter's triad is not an IgE mediated hypersensitivity reaction. Rather, this intolerance is likely a result of abnormal arachidonic acid metabolism with a modulation of eicosanoid production.[56,66-68] The inhibition of the cyclo-oxygenase pathway leads to metabolite diversion to the lipoxygenase pathway with decreased levels of anti-inflammatory prostaglandins, particularly PGE2. As a result, there is an increase in the cysteinyl leukotrienes, A4, B4, C4, D4, and an increase in leukotriene C4 synthase. Overall, there is excessive production of leukotrienes that lead to the inflammatory reaction.[66,69]

The histopathology seen is the same persistent inflammation of the lower airway as that seen in other forms of chronic asthma. Evidence of mast cell activation is seen. There is marked eosinophilia, epithelial disruption, and cytokine production. Bronchial biopsy specimens from aspirin-sensitive patients show a 4-fold greater number of eosinophils than in aspirin-tolerant patients and a 15-fold greater number as compared with normal mucosa.[67] There are also high levels of interleukin-5, RANTES, and eotaxin.[48]

The definitive way to diagnose aspirin intolerance is by provocation. Oral ingestion is most common; other routes are topical nasal administration, bronchial inhalation, or via intravenous administration. This is cautiously done when suspicion is high for those patients who have not yet been diagnosed.

Treatment is targeted at the control of disease in both the upper and lower airways. Above all, avoidance of aspirin-containing products is undertaken. Treatment of the lower respiratory disease associated with aspirin intolerance is the same as for other forms of asthma with medical therapy. Surgery is frequently used to help control CRS and sinonasal polyps. Despite aggressive medical and surgical treatment, polyps tend to recur and multiple surgical procedures are commonly performed.[48]

Like that seen in aspirin-tolerant patients, subjective and objective improvement of asthma is seen after sinus surgery. Statistically significant improvement in pulmonary function tests continued to be seen for 1 year postoperatively in a study of 20 patients by Nakamura et al.[70] Many of these patients were able to reduce their doses of inhaled corticosteroids postoperatively as well.

Aspirin desensitization is frequently reported to have a beneficial effect on the clinical manifestations of Samter's triad. Desensitization involves initial incremental dosing with eventual daily high dose administration of aspirin. Continuous intake of aspirin is maintained indefinitely. The mechanism of desensitization therapy is unclear. Proposed alterations include reduced production of thromboxane B2 as a product of COX-1 and COX-2, the modulation of arachidonic acid metabolism, and diminished leukotriene receptors.[66]

Though there are few randomized studies, the majority of studies that examine aspirin desensitization show clinical benefit overall in both the upper and lower airway. Improvement in asthma, rhinosinusitis, and control of sinonasal polyps is seen. There has been a reported decreased need for oral and inhaled steroid use. Unfortunately, gastritis can lead to discontinuation of therapy.[66,68] The intranasal administration of lysine-aspirin for desensitization has been tried with promising results.[71]

ASTHMA AND ATOPY

As has been discussed above, studies consistently indicated a relationship between allergic rhinitis and asthma. These studies suggest that allergic rhinitis, rhinosinusitis, and asthma are manifestations of an inflammatory process within a continuous airway.[72] Among patients with asthma, the majority have evidence of IgE-mediated sensitivity to airborne allergens.[5] In addition, allergen avoidance has been shown to result in a reduction of nonspecific bronchial hyperresponsiveness, improvement of asthma symptoms, and reduction in use of medications.[73] In general, the more persistent and severe the rhinitis, the more likely that asthma will be present and symptomatic.[5]

Risk Factors that Predispose to Atopy and Persistent Asthma

Early sensitization to inhalant allergens is a strong risk factor for subsequent development of atopic diseases during childhood. Not all atopic patients, however, will progress to the development of asthma. Population-based studies suggest that although up to 40% of young children manifest skin reactivity to 1 or more inhalant allergens, only about 25% of these individuals progress to clinically apparent asthma over time.[74] Nonspecific subclinical bronchial hyperreactivity is common in many patients with allergic rhi-

nitis.[75-77] Rhinitis frequently predates the onset of asthma, and those with allergic rhinitis and bronchial hyperreactivity are more likely to develop asthma.[78] One commonly recognized atopic trigger is exposure to cats in high-risk individuals. A recent study demonstrated that increased exposure to cats results in a significantly increased development of asthma. This findings is particularly noted in the children of asthmatic mothers.[79]

Immunology: Sensitization and the Immune Response

Allergen-specific T-helper-2 (Th2) responses with the subsequent release of interleukins such as IL-4, IL-5, and IL-13 are responsible for the cascade of events necessary for allergic inflammation. It appears that genetic and environmental influences in early life are critical in the definition of the patterns of immune response involved in allergy and asthma. Initial priming of T-helper cells against environmental allergens commonly occurs in utero, presumably by means of transplacental transport of allergens to which the mother is exposed during pregnancy. These early allergen-specific responses are dominated by production of the same Th2 cytokines that are associated with expression of atopy and asthma in later life.[80]

In contrast, inhalant antigen exposure during infancy and early childhood results in either a redirection of these responses toward a Th1-like cytokine pattern (in nonatopics), a process termed immune deviation, or in a further boost of the fetally primed Th2-polarized immunity in potential atopics. The increasing tendency for failure of this allergen-driven immune deviation process during early life seems to lie at the core of the progressively rising prevalence of atopic disease.[81] A possible cause that accounts for the failure of this allergen-driven immune deviation mechanism is a reduced capacity in some infants to produce the Th1 cytokine interferon gamma. This process may compromise their ability to develop normal patterns of Th1-like immunity against inhalant allergies. Other possibilities include defects in serum opsonization and in secretory IgE production,[74] which suggests a generalized low-level deficiency in immune function. Because microbial stimulation is felt to be the principal stimulus for normal postnatal maturation of the Th1 cell,[82] it has also been proposed that reduced microbial exposure in early life can lead to the polarization of allergen-specific T-cell memory and a Th2-skewed immune response.

In a prospective birth cohort study[83] of over 1000 children, the relative risk of frequent wheezing was assessed among those children with older siblings in a school environment and among those who had attended daycare as infants. Initially the children with the increased exposure to possible infection had a significantly greater risk of frequent wheezing as opposed to those with less infection exposure. However, after the age of 6, children with high exposure were significantly less likely to wheeze than those with low exposure. It is believed that circumstances that expose young children to infections may actually protect against the development of asthma and frequent wheezing later in childhood.[83] It is unclear if reduced microbial exposure is the only environmental stimulus that influences this immune effect, but this particular environmental exposure has receive the most attention.

In general, prospective studies indicate that the development of atopic symptoms by the age of 2 years is associated with progressive upregulation of Th2-like immunity to inhalants, particularly in high-risk subjects, whereas those who remained symptomfree developed a more Th1-like response pattern.[84]

THE EPIDEMIOLOGY OF ASTHMA

The epidemiology of asthma is an area of research that is complex and essential to the understanding of a disease that has a significant impact on the morbidity and mortality of a large number of patients. The complexity is due to the lack of a widely accepted definition of asthma that is both pathophysiologically and clinically acceptable. The American Thoracic Society first defined asthma in 1962 as a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.[85] In 1975, the World Health Organization described asthma as a chronic condition characterized by recurrent bronchospasm resulting from a tendency to develop reversible narrowing of airway lumina in response to stimuli of a level or intensity that would not cause such narrowing in most individuals. Finally, in 1991, the National Institutes of Health and National Heart Lung and Blood Institute described asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. It is clear now,

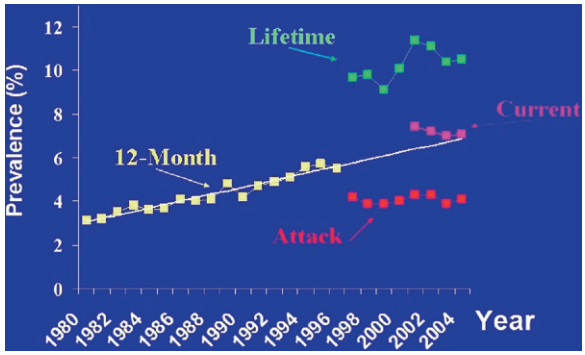

Figure 2 Asthma prevalence in the United States, 1980-2004. Data was based on the respose to 1 question: "Have you had an asthma attack within the past 12 months?" More recently, 3 questions have been used in the survey: 1) "Have you ever been told by a physician that you have asthma?" (lifetime), 2) "Do you still have asthma?" (current), and 3) "Have you had an asthma attack within the past 12 months?" (attack). (Source: National Health Interview Survey, National Center for Health Statistics.)

after years of research, that it is chronic inflammation that causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.

It is difficult to compare epidemiologic studies over the past 40 years because of these changing definitions. It is not clear who truly had asthma when they were included in these evaluations. Furthermore, most epidemiologic studies rely on self-reporting by patients with respect to whether they have a diagnosis of asthma, and the questions used in these surveys have changed over the years, further confounding the data.

Most of the data on the prevalence of asthma within the United States are derived from the National Health Interview Survey, a yearly survey conducted by the National Center for Health Statistics. From 1980 to 1996, the determination of asthma prevalence relied on a self-reported occurrence of at least 1 asthma attack within the preceding 12-month period. The prevalence of asthma increased 73.9% during that time period, with an estimated 6.9 million people reporting an episode of asthma in 1980, in comparison with 14.6 million people in 1996. There are many factors postulated to be responsible for this increased prevalence, mostly related to identified risk factors for asthma, and these will be discussed later in this supplement.

In 1997, the asthma questionnaire was changed to include a new measure of asthma prevalence. Respondents were now asked about lifetime asthma prevalence with the question, "Have you ever been told by a health care professional that you have asthma?"[2] In this year, the prevalence of asthma was reported to drop to 11.1 million (20% decrease from 1996), but this can be attributed to the change in the questionnaire. The requirement that the patient have a diagnosis of asthma from a health care professional may have led to more accurate information with respect to the diagnosis of asthma in each individual.[86]

At the present time, the National Health Interview Survey includes a third question with respect to asthma prevalence: "Do you currently have a diagnosis of asthma?" On the basis of the responses to this question, the prevalence of asthma seems to be stabilizing over the past 5 years at approximately 7% of the U.S. population (Fig 2).

Table 5
Asthma prevalence by age

Age and sex	Percent	95% Confidence interval
0-14 Years		
Total	9.0	8.30-9.68
Male	10.5	9.49-11.47
Female	7.4	6.58-8.29
15-34 Years		
Total	7.7	7.09-8.32
Male	5.8	5.07-6.62
Female	9.6	8.64-10.51
35 Years and over		
Total	7.4	6.96-7.78
Male	5.2	4.61-5.73
Female	9.3	8.78-9.91
All ages: crude		
Total	7.8	7.50-8.10
Male	6.5	6.11-6.93
Female	9.0	8.61-9.44
All ages: age adjusted		
Total	7.8	7.51-8.11
Male	6.5	6.09-6.90
Female	9.0	8.59-9.41

Prevalence of current asthma among persons of all ages, by age group and sex: United States, 2005 (Data from the Centers for Disease Control. Available at: www.cdc.gov/nchs/data/nhis/earlyrelease/200606_15.pdf.

Asthma, Gender, and Age

The epidemiology of gender and asthma reveals that in children aged 6 to 11, the male to female ratio is approximately 3:2 for affected individuals. Older children (aged 12 to 17) have a male to female ratio of 8:5.[87] There have been several proposed reasons for this gender difference; the most likely is that males have smaller airways for a given lung size than females.[88] This difference in airway anatomy may predispose boys to more wheezing and lower respiratory illness. As asthmatic patients move into adulthood, the gender ratio reverses, with more females affected than males. This would also suggest that females with asthma in childhood may be more likely to have persistent disease as an adult.

The prevalence of asthma in the United States is consistently higher in children, when compared with adults. The data from the 2005 National Health Interview Survey[89] reveal the prevalence in children 14 years of age and younger to be 9.0%, compared with adults with a prevalence of 7.8%. Once again, airway anatomy and physiology is believed to be a major etiologic reason for this finding.

Table 5 displays the most recent prevalence data on asthma from the 2005 National Health Interview Survey. These numbers are based on the question, "Do you currently have asthma?" Once again, we can see great discrepancies between adults and children as well as between males and females. The overall prevalence of 7.8% is roughly equivalent to 23 million Americans with asthma, 6.2 million are under the age of 18.

Asthma and Risk Factors

Race and income level. The prevalence of asthma under the age of 14 is highest in the African American population (13.6%), followed by Hispanics (9.2%), and then whites (7.5%). Over the age of 14, the prevalence remains highest in African Americans (8.4%), followed by whites (7.7%), and then Hispanics (5.3%).[89]

The low prevalence in Hispanics is actually deceiving. In fact, Hispanics of Mexican heritage have the lowest asthma prevalence of any racial group, whereas Hispanics with

Puerto Rican heritage have the highest prevalence of any group, 30% higher than that of the African American population and 100% higher than whites.[90] This interesting fact has led to speculation on the role of genetics in the natural history of asthma, as this clearly must be a factor.

The well-documented increased prevalence of asthma in the African American community has been hypothesized to be due to decreased access to health care, and perhaps low income level. Income level has been addressed by the National Health Interview Survey and reveals that asthma prevalence in patients living below the poverty line is significantly higher than any other income level. This assessment of income level did not take race into consideration. As an extension of this, asthma prevalence in urban versus rural settings was examined as well. Surprisingly, there was no significant difference between urban and rural patients with respect to the prevalence of asthma. In fact, the trend was toward a slightly higher prevalence in the rural population.

The connection between race, income level, and asthma prevalence has been evaluated in several independent studies. An analysis of the data from the National Health Interview Survey in 1997 examined the independent and joint effects of race and income-to-federal poverty level ratio on asthma prevalence. The overall prevalence of asthma was highest in African American children at 13.6%, compared with whites at 11.2%, and the highest prevalence was noted in African American children living at less than half the federal poverty level.[91] This difference was significantly different when compared with all races at higher income levels.

A survey conducted in Los Angeles in 1999 and 2000 evaluated 6004 children under the age of 17 for asthma and income level. The prevalence of asthma was greatest in the African American children from low-income families.[92] It is clear that the population at greatest risk for asthma is African American children from poor urban neighborhoods. This has served as a focus point for early intervention strategies and includes patient and family education as well as improving access to health care. The Harlem Children's Zone Asthma Initiative[93] is an example of such an effort that has been ongoing in New York City for several years. This plan has led to improved asthma control, medication compliance, and decreased absenteeism and hospitalizations.

Environmental smoke. There seems to be an increased risk of early onset asthma in children exposed to tobacco smoke with an increased incidence of wheezing until age 6.[94] The National Health Interview Survey data collected in 1981 indicate an increased risk of asthma in children under the age of 5 whose mothers smoked at least one half pack per day.

An analysis[95] of 451 nonsmoking adults with asthma who were exposed to second-hand smoke divided the subjects into 3 groups: 1) those with exposure at baseline but none at follow-up, 2) those with no baseline exposure but with new exposure, and 3) those with exposure both at baseline and at follow-up. Patients with baseline environmental tobacco exposure had higher asthma severity scores, increased emergency department visits, and increased risk of hospitalization. The subjects who were able to remove themselves from the second-hand smoke exposure had improved quality of life scores and decreased emergency department visits. Environmental tobacco exposure is a highly significant risk factor for asthma and can increase the severity of disease.

Obesity. In the United States, the prevalence of obesity has increased from 13.4% among men aged 20 to 74 years in 1962 to 27.6% in 2002 and from 15.8% to 33.2% in women.[96] As aforementioned, the prevalence of asthma increased 73.9% between 1980 and 1996. The concurrent increases in these 2 conditions raises the possibility that the 2 might be connected.

A significant association between excess weight and asthma incidence has been shown in several prospective studies. Population surveys suggest that patients with asthma are disproportionately obese compared with people who have never had asthma. Furthermore, weight loss studies have shown substantial improvements in the clinical status of many obese patients who lose weight.[97]

The cause behind this seeming connection between obesity and asthma remains a mystery. Several mechanisms have been postulated, including mechanical effects and immunologic correlates of obesity. A shared genetic basis for both has also been proposed. Increased serum leptin levels is one proposed mechanism that holds a great deal of promise. Leptin is a hormone produced by adipocytes that acts at the hypothalamus to signal satiety and increase metabolic rate. Serum leptin levels are elevated in obesity. Interestingly, leptin is a member of the IL-6 family of cytokines, with its associated effects on inflammation. It can also trigger the sympathetic nervous system. All of these may significantly impact lung function. Leptin may be the missing link between obesity and asthma, but further research is required.[98]

Respiratory infections. The impact of respiratory infections on the asthma incidence is an area of debate. The hygiene hypothesis suggests that exposure to airway infections and allergens at a young age would predispose to the development of a TH1 immune response, thereby avoiding the TH2 cytokine profile and decreasing the incidence of asthma or allergic disease. Studies on daycare attendance and subsequent development of asthma support this hypothesis, as they have shown increased lower respiratory illnesses and recurrent wheezing at a young age, but decreased development of asthma later in childhood for those who attended daycare.[99] However, other studies contradict this.

Lower respiratory tract infections in the first 3 years of life significantly increase the risk of a child developing asthma when evaluated prospectively at both age 6 and 11, with most infections caused by viruses.[100] Mechanisms have been proposed to describe this relationship between viral respiratory infections and the subsequent development of asthma. It has been suggested that respiratory syncytial virus (RSV) may directly induce long-term changes in the

lower airways, whereas others have provided evidence that decreased levels of lung function are present at birth in these "at-risk" children, and this abnormality predisposes them to wheezing and airway obstruction during viral respiratory infections in early life.[101] It does seem that a significant lower repiratory infection before the age of 3 is a risk factor for subsequent development of asthma.

Other risk factors for asthma have been identified. Air pollution, both indoor and outdoor, have been linked to increased risk of asthma and increased disease severity, much as is the case with environmental tobacco smoke exposure. Prematurity, and particularly bronchopulmonary dysplasia, are highly linked to the development of asthma. Atopic disease and genetics both have complex relationships with asthma and will be discussed below.

Asthma Morbidity

Morbidity and Mortality Weekly reports on asthma every year. This publication of the Centers for Disease Control examines asthma prevalence, school and workdays lost, activity-limitations due to disease, outpatient physician visits, hospitalizations, emergency department visits, acute asthma attacks, and asthma deaths. These data are extremely important to take into consideration when discussing the burden of asthma on our patients and society.

In 2002, there were 13.9 million outpatient visits for asthma. These visits were most common in children under the age of 17 (687 per 10,000) compared with patients over the age of 18 (181 per 10,000).[102] There were no racial differences in these scheduled outpatient appointments for asthma. One thing that is clear from this data is that while the prevalence of asthma may be stabilizing, health care use continues to increase.

Unscheduled visits to the emergency department for asthma were at an alarmingly high level of 1.9 million visits in 2002. Children under the age of 17 had a rate of 100 per 10,000, with the highest frequency of visits for patients under the age of 4. These emergency department visits were 4 times higher for African Americans with a rate of 217 per 10,000 as compared with whites at a rate of 45 per 10,000. This fact once again raises the question of poor access to health care for the African American community, with less than optimal control of disease.[102]

Hospitalizations for asthma have increased 200% in children and 50% in adults from 1960 to 1980. In the 1990s, adult admissions continued to increase. Data from the National Hospital Discharge Survey in 2002 revealed that 17 per 10,000 admissions were for asthma, or roughly 484,000 people; 187,000 of these were children. The average length of stay was 3.2 days, and asthma hospitalization occurred at the highest rate for children under the age of 4 (59 per 10,000). African Americans were hospitalized at a 225% higher rate than whites.[102]

The Asthma in America Survey[103] was a study of 2500 adults with asthma, or caregivers of children with asthma, followed for a 12-month period. During this yearlong period, 50% of children missed school, 25% of adults missed work. 23% were seen in an emergency department, 29% saw their physician urgently, and 9% were hospitalized. Overall, 41% of adults and 54% of children required a physicians care in some form. Study subjects also reported significant limitation of their activity level due to asthma. It is clear that productivity is significantly affected by asthma.

The financial burden of asthma is significant. The current estimate of the cost of medical care is approximately $1300 per patient per year for asthma. Asthma-related costs have increased by over 50% during the time period of 1984 to 1994 and continue to rise due to improved medications and better use of them, as well as indirect costs that relate to lost productivity. In 1994, the total direct and indirect costs in the United States was 12 billion dollars.[104] It is important to remember that individual patient costs are related to the severity of disease, as only 10% to 20% of patients have severe asthma, but this accounts for 50% of the costs.

Asthma Mortality

Asthma deaths are rare, particularly under the age of 15. In 1978, the mortality rate from asthma was 0.8 per 100,000. This increased to 2 per 100,000 in 1989 and then 2.1 per 100,000 in 1994. In the year 2000, there was a sharp drop in the mortality rate to 1.6 per 10,000. This decrease was partially due to a change in coding on death certificates, so that asthma was no longer grouped with other chronic pulmonary diseases. However, statistical analyses have shown that this change alone cannot account for the total decrease.[105] There does seem to be a true decrease, probably because of improved medications, health care access, and patient education. In 2002, the mortality rate had decreased even further to 1.5 per 100,000 (0.3 per 100,000). However, racial disparities are evident in these figures as well, with a mortality rate for African Americans of 3.7 per 100,000, a figure which is 200% higher than the asthma mortality in whites.

PATHOPHYSIOLOGY OF ASTHMA

A basic understanding of the pathophysiology of asthma begins with a definition. The specific definition of asthma, however, has been evolving over the last 30+ years. In the 1970s, the World Health Organization defined asthma as a chronic condition characterized by recurrent bronchospasm secondary to reversible narrowing of the airway lumen. In another classification, asthma was further conceptualized as a disease in which the primary pathophysiology related to airway constriction, with symptomatic expression demonstrated throughout wheezing and dyspnea. Rees[106] in 1984 described asthma in the following manner: "The characteristic feature of asthma is reversibility of airflow obstruction over short periods of time, usually either bronchoconstriction in response to specific stimuli or bronchodilatation in response to treatment." Further, Rees defined asthma as "a disease characterized by wide variations over short periods of time in resistance to airflow in intrapulmonary airways."

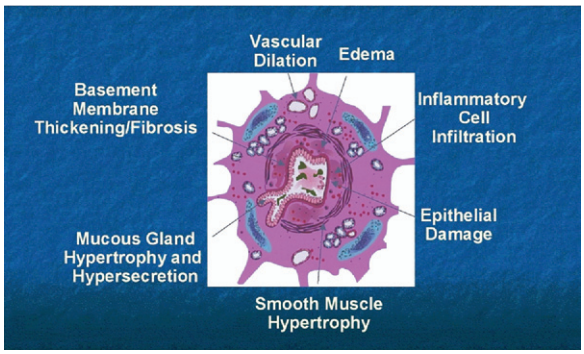

Figure 3 Physiologic changes in asthma.

There was no reference in these systems to the nature of asthma as an inflammatory disease.

One can see that this definition was based on the understanding at the time that asthma was a disease specifically characterized by airway obstruction and was associated with reversible narrowing of the airway lumen. Over the years, the definition of asthma has evolved to incorporate the central role of inflammation, and in 1991 the National Heart, Lung, and Blood Institute[107] defined asthma as:

"A lung disease with the following characteristics:

- Airway obstruction that is reversible
- Airway inflammation
- Increased airway responsiveness to a variety of stimuli."

As our understanding of the role of inflammation in asthma has evolved, its definition has also evolved to include the fact that asthma is not only associated with reversible airway obstruction, but that airway inflammation has become a critical component of asthma. This inflammation is specifically associated with an increased airway responsiveness to various triggers that lead to the symptomatic expression of asthma. One of the more recent definitions of asthma is from the National Asthma Education Prevention Program[108] in 1997, which defined asthma as "a chronic inflammatory disorder of the airways with many cells and cellular elements playing a role, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells." This newer definition of asthma also includes the fact that the inflammation associated with asthma is always present to some degree regardless of the level of asthma severity and that environmental and other factors "cause" or "provoke" the airway inflammation in patients with asthma. The understanding that airway inflammation is always present in asthma leads to a model of the disease that illustrates that asthma symptoms are only the tip of the iceberg. Airway inflammation leads to bronchial hyperresponsiveness that results in airway obstruction and subsequent symptoms.

The pathophysiologic process involved in asthma is dependent on chronic inflammatory changes in the bronchial mucosa. These inflammatory events lead to edema of the airway mucosa as well as a variety of concurrent events. These pathophysiologic changes in asthma are illustrated in Figure 3, which demonstrates the role of edema around the bronchial airways accompanied with vasodilatation, inflammatory cell infiltration, damage to the bronchial epithelium, smooth muscle hypertrophy in the airways, mucous gland hypertrophy and hypersecretion, and ultimately basement membrane thickening and fibrosis.

A physiologic definition would also include the fact that asthma is a chronic inflammatory disorder of the airways and that this inflammation is associated with airway hyperresponsiveness, airflow limitation, and respiratory symptoms. Our understanding of asthma as an inflammatory disorder does have implications for the diagnosis, prevention, and management.[109] These changes are illustrated in Figure 4, which compares a normal bronchial mucosa with an asthmatic bronchial mucosa.[110] This basement membrane thickening has been characterized particularly in more severe, persistent asthmatic patients, particularly with chronic asthma.

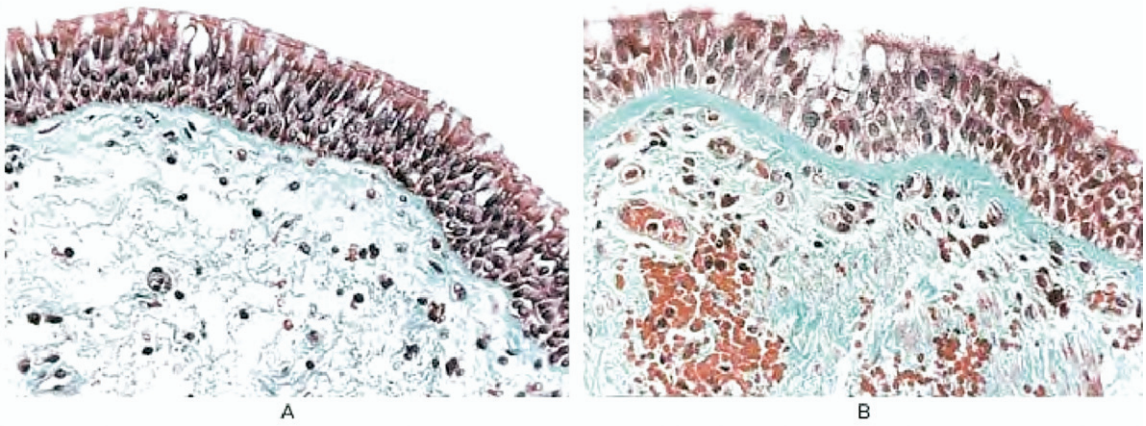

Figure 4 Histologic changes in asthma compares (**A**) normal bronchial mucosa with (**B**) an asthmatic bronchial mucosa and clearly illustrates cellular infiltration, the mucosa hypersecretion, epithelial hypertrophy, and most specifically, basement membrane thickening with fibrosis. (Adapted from Busse WW, Lemanske EF. Asthma. N Eng J Med 2001;344:350–362.) Reproduced with permission.

Other studies have demonstrated that the thickness of the basement membrane is increased in asthma, particularly with chronic asthma symptoms and, to a lesser degree, in patients with seasonal asthma.[111] There is also evidence of basement membrane thickening in asthmatics, even when they are in remission. Van den Toorn et al[112] have demonstrated that basement membrane thickness in airway biopsies is similar in asthmatics whether they have active disease or are in remission, when those biopsies are compared with control patients.

Another pathophysiologic feature of asthma is its relationship to total IgE level. Interestingly, there has been clear demonstration that elevated IgE is associated with airway hyperactivity. Sunyer et al[113] demonstrated in 203 patients with acute asthma who were seen in the emergency room over a 2-year period that the odds ratio for bronchial hyperactivity was clearly increased in patients who had higher total serum IgE levels.

In addition, airway inflammation in asthma is also accompanied by cellular infiltration and increased numbers of eosinophils in the patient's sputum. Louis et al,[114] in 2000, reported a significant correlation between asthma severity and sputum eosinophilia in patients with chronic asthma. Airway hyperactivity has also been correlated with severity of asthma. Patients with mild asthma have required higher concentrations of methacholine to trigger a fall in FEV-1 by 20% (PC 20) compared with those patients with moderate to severe persistent asthma.

Another finding in asthmatics that is correlated with severity is the level of cysteinyl leukotrienes in patient's sputum. Pavord et al[115] reported that the severity of asthma correlates with levels of cysteinyl leukotrienes present in induced sputum, with leukotriene levels higher in patients who experience acute asthma attacks and those with persistent asthma than in patients with chronic stable asthma under control and in normal controls.[115] Cysteinyl leukotrienes have been associated with decreased mucous transport, epithelial cell damage, eosinophil influx, increased mucous hypersecretion, edema of the blood vessels in the bronchioles and smooth muscle hypertrophy and constriction of small airways.

Factors that influence persistent wheezing and asthma include both genetic and environmental variables. Genetic factors include predisposition for atopy, which may involve cytokine deregulation. Environmental factors include exposure to allergens and irritants, as well as early respiratory infections. Th2 cytokine responses are present in the majority of patients with active asthma, and the balance of Th2 and Th1 responses is involved in the predisposition to develop asthma and other atopic diseases. Factors that favor a Th2 phenotype, which tends to be associated with allergic disease and asthma, include urban environment and Western lifestyle, sensitization to house dust mites and cockroaches, frequent use of antibiotics and vaccines, and only 1 child in the home. Factors associated with Th1 phenotype, which tends to reduce the risk of allergic diseases and asthma, include the presence of older siblings in the home, early exposure to daycare and respiratory illnesses, other chronic illnesses, such as tuberculosis, hepatitis A and measles, and living in a rural environment, particularly around animals.[110] Support for this observation was demonstrated in a study[116] that found an inverse relationship between the amount of endotoxin load found in mattresses and the prevalence of allergic asthma and wheezing. Nonallergic wheezing and respiratory symptoms, however, did not appear to correlate with endotoxin load in the environment.

A working knowledge of the pathophysiology of asthma is essential in understanding the classification system for asthma described by the National Heart, Lung, and Blood Institute (NHLBI).[117] These guidelines describe the severity and chronicity of asthma in 4 categories including mild intermittent, mild persistent, moderate persistent, and severe persistent. These categories are determined by symptoms and objective findings, such as lung function, and will be discussed in detail later in this supplement. As seen in the aforementioned studies, there appears to be a clear correlation between the severity of asthma and the presence of inflammatory mediators, including eosinophils, cysteinyl leukotrienes, basement membrane thickening, and airway hyperactivity with the severity of asthma. An understanding of the pathophysiology of asthma and an appreciation of the central role of inflammation in this disease are essential in guiding appropriate and efficacious treatment.

ASSESSMENT OF ASTHMA

Clinical Presentation

As has been previously discussed, asthma is an inflammatory, lower respiratory, reactive airway disease that presents with the classic manifestations of cough, wheeze, and chest tightness, or shortness of breath. In many patients, it is possible that their only symptom is coughing, as in the case of cough-variant asthma. Another physical presentation of asthma can be nocturnal awakening. These symptoms are recurrent and often severe enough to affect one's daily routine and activity.[107]

The physical manifestations of asthma are repetitive and often occur with exposure or re-exposure to specific triggers.[107] Such triggers can include upper respiratory viral infection, inhalant allergen exposure, exercise, inhalant irritants such as smoke, cold dry air, strong emotion, or laryngopharyngeal reflux. Because exacerbations of lower respiratory tract symptoms are commonly initiated by these stimuli, asthma can be worse during certain times of the year when stimuli are present seasonally, or it can be relatively constant throughout the year with perennial provoking agents. Between episodes of provocation, the patient may be asymptomatic. If the airway obstruction is persistent, however, the patient's complaint can also be persistent and may not resolve until medical treatment is initiated.

Because the airway constriction in asthma is reversible and variable, the obstructive component of the disease can improve after removal of an inciting trigger or with bron-

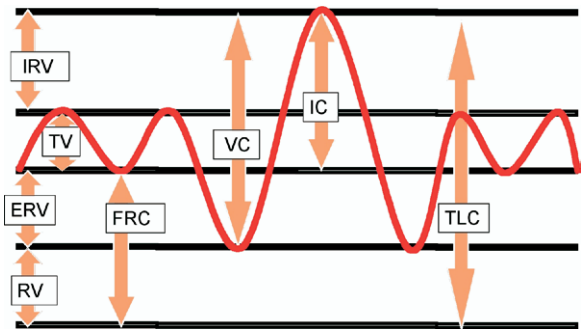

Figure 5 Subdivisions of lung volumes. (IRV, inspiratory reserve volume; TV, tidal volume; ERV, expiratory reserve volume; RV, residual volume; FRC, functional residual capacity; VC, vital capacity; IC, inspiratory capacity; TLC, total lung capacity.)

chodilating medications. These bronchodilators, however, have no effect on the underlying inflammation at the core of the disease pathophysiologically. Asthma is a chronic process and is often accompanied by acute exacerbations of symptoms among patients with persistent disease. In these individuals, persistent low levels of symptoms can worsen with exposure to stimuli. As such, asthma is characterized by recurrent acute episodes.[108]

Because asthma is an inheritable disease, it is important to elicit a family history of asthma or allergy on evaluation. Also asthma is likely to be present with other allergic disease processes as well.

Physical Examination

Physical findings in the patient with asthma include wheezing, coughing, prolonged forced expiration, hyperexpansion of the chest, and use of accessory muscles with supraclavicular retraction on inhalation. Coughing can often produce copious amounts of thick tenacious mucous. On percussion of the lung, the chest is hyper-resonant because of air trapping in the lung. Tachycardia and tachypnea are frequently present.

Asthma often coexists with other allergic diseases such as atopic dermatitis, eczema, and allergic rhinitis. Therefore physical findings such as hypertrophic nasal turbinates and skin irritation should be sought. On laboratory testing, patients with inhalant allergens can have elevated IgE and a positive wheal reaction to skin testing. Because the airway obstruction is variable, shortness of breath or wheezing may not be present at the time of the examination. Absence of recent symptoms or current physical findings, therefore, does not exclude the diagnosis of asthma.

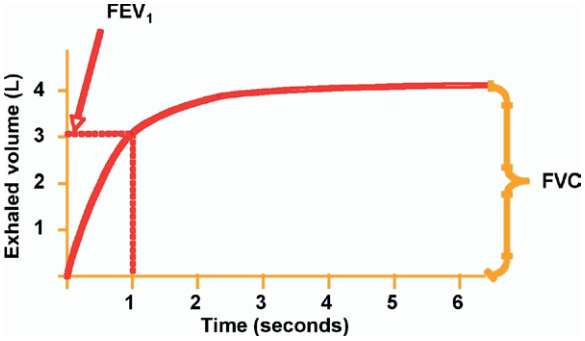

Figure 6 Normal spirometry. (FEV_1, forced expiratory volume within 1 second; FVC, forced vital capacity.)

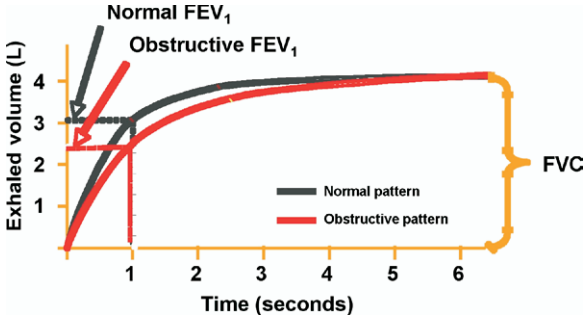

Figure 7 Comparison of obstructive pattern to normal spirometry. Note low FEV_1 and normal FVC. (FEV_1, forced expiratory volume within 1 second; FVC, forced vital capacity.)

Pulmonary Function Testing

It is difficult and inaccurate to attempt to measure or quantify objectively the degree of lower airway obstruction from history and physical examination alone; pulmonary function testing is needed to assess the physiologic status of the lungs. Pulmonary function testing can confirm the clinical diagnosis of asthma, determine if current lung function is normal or abnormal, and categorize the nature of pulmonary disease as either obstructive or restrictive. Objective pulmonary testing can also be conducted to follow the progression and severity of pulmonary disease. In other words, quantitative pulmonary assessment can be used to measure the response to medical treatment so that the therapy can be maintained or changed as needed.

Several methods can be used to evaluate pulmonary function. Different types of pulmonary function measures include assessment of lung volumes, spirometry, flow-volume loop, diffusion capacity, and body plethysmography. Lung volumes can be calculated with body plethysmography, helium dilution, or open circuit nitrogen washout. The

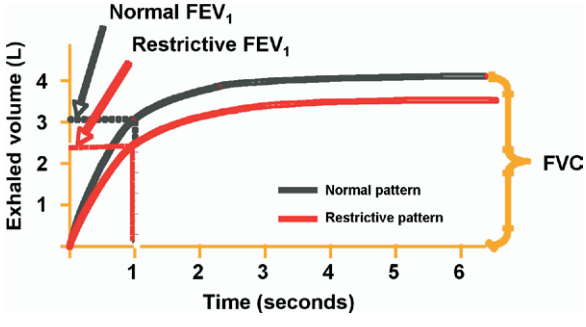

Figure 8 Comparison of restrictive pattern to normal spirometry. Note low FEV_1 and low FVC. (FEV_1, forced expiratory volume within 1 second; FVC, forced vital capacity.)

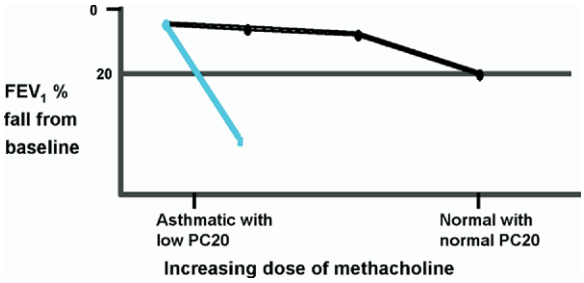

Figure 9 Drop in FEV_1 of 20% (PC20) in response to bronchial challenge with methacholine.

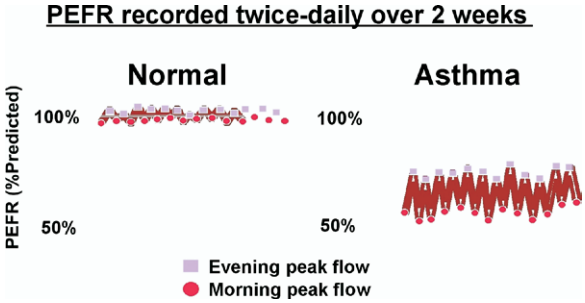

Figure 11 Circadian changes of peak expiratory flow rate (PEFR).

different subdivisions of lung volumes are depicted in Figure 5. Total lung volume or capacity is dependent on inspiratory muscles, whereas the expiratory muscles influence the residual volume. Tidal volume is the volume of air movement during quiet breathing. Vital capacity is the largest amount of air movement during a single breath. Residual volume is the remaining amount of air in the lung after complete exhalation. Asthmatics have increased reserve volume due to air trapping and therefore less vital capacity.

Pulmonary function tests that best evaluate asthma, which is a disease of small airways, are spirometry and flow-volume loops. Together these tests evaluate forced expiratory vital capacity (FVC). FVC can be measured either by volume-time plots (spirometry) or flow-volume loops. Spirometry is measured in units of liters per second. The amount of air that is exhaled within the first 1 second of expiration during spirometry is known as forced expiratory volume (FEV_1) (Fig 6).

Forced vital capacity testing can differentiate between obstructive versus restrictive pathology on the basis of the FEV_1 and FVC values. Normally, 95% of forced vital capacity can be exhaled within 3 seconds in forced vital capacity testing. For pulmonary obstructive disease, as in the case of asthma, there is a reduction in the FEV_1 but not in the FVC (Fig 7). Restrictive airway disease has both a reduced FEV_1 and FVC (Fig 8). For restrictive disease, it is reduced total lung capacity that then reduces vital capacity.

Measured values from spirometry can be used to evaluate the severity of obstruction. One value is FEV_1, which is the most sensitive indicator to assess lower airway obstruction. The predicted value of a FEV_1 based on gender, age, height, and weight can be used to determine the severity of obstruction. A predicted value of FEV_1 between 70% to 85% is considered mild obstruction, 60% to 69% is moderate, 50% to 59% is moderate severe, 35% to 49% is severe, and less than 35% is very severe.[118]

Because the lower respiratory airway obstruction in asthma is reversible, there should be a resolution or improvement of the obstruction with a bronchodilator. An increase of 12% for the FEV_1 by a bronchodilator is suspicious for asthma. However, this value cannot be used as the sole diagnostic criterion for asthma. Spirometry values used in conjunction with symptoms and level of function also assist with confirmation of the presence of asthma.

As discussed earlier, obstruction of the lower airways is triggered by reversible bronchoconstriction with exposure to various stimuli. Another method to confirm the diagnosis of asthma, therefore, is to challenge a patient suspected to have asthma with an irritative airway stimulus such as methacholine or histamine. This test to stimulate and assess airway reactivity is known as pulmonary challenge or bronchial provocation. The concentration of the pharmacologic agent needed to decrease the FEV_1 by 20% from the baseline is defined as the PC_{20}. In asthmatic patients, the PC_{20} is lower than in the normal population (Fig 9), which demonstrates that the asthmatic airway is more responsive to challenge than the normal airway. As with FEV_1, however,

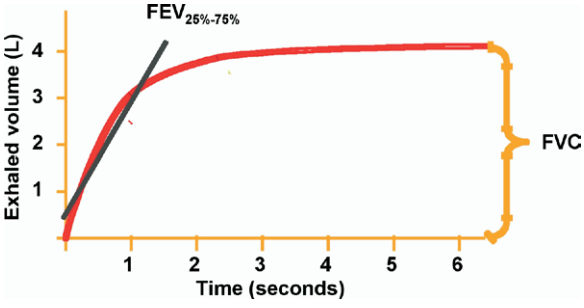

Figure 10 $FEV_{25\%-75\%}$ represented by the slope between the first 25% and 75% of expiration.

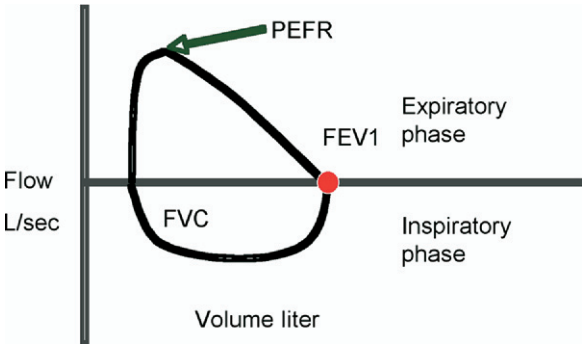

Figure 12 Normal flow-volume loop. *Top line* represents the expiratory phase and the *bottom line* the inspiratory phase. *Dot* represents the start of inspiration. (PEFR, peak expiratory flow rate.)

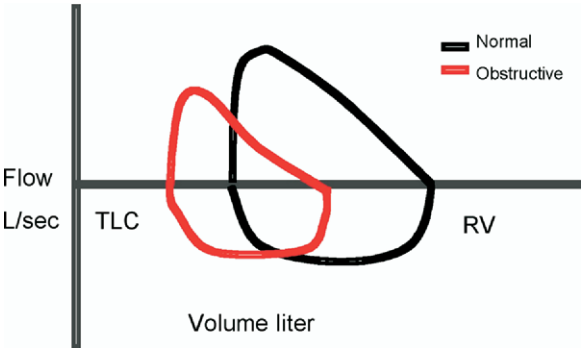

Figure 13 Normal flow-volume loop compared with obstructive flow-volume loop. (TLC, total lung volume; RV, residual volume.)

having a low PC_{20} alone does not give the diagnosis of asthma, although it does increase the suspicion of the presence of asthma.

A good measure to describe a pulmonary pathoses is the ratio of FEV_1 to FVC. For obstructive disease, this ratio is usually decreased. For restrictive disease, this ratio is normal or increased. The FEV_1/FVC ratio greater than 75% is generally considered normal, however, this ratio is not a good indicator for severity of airway obstruction because patients with asthma can have a normal FEV_1/FVC ratio.

A sensitive measurement to evaluate airway obstruction is $FEF_{25\%-75\%}$, which is forced expiratory flow between 25% and 75% of the FVC (Fig 10). This parameter measures the mean rate of airflow over the middle half of the FVC. Therefore $FEF_{25\%-75\%}$ targets the measurement of small airways during expiration. $FEF_{25\%-75\%}$ can be more sensitive than FEV_1, so an FEV_1 value can be normal but $FEF_{25\%-75\%}$ can be decreased. A value greater than 65% is considered normal for $FEF_{25\%-75\%}$. Because $FEF_{25\%-75\%}$ can be overly sensitive, it cannot be used to define the severity of lower airway obstruction.

It is difficult to perform spirometry in children less than 4 years, and for some children spirometry may not be able to be performed adequately until age 7 years. An alternate method to estimate airway obstruction, therefore, is to record peak expiratory flow rate (PEFR) (Fig 11) in the morning and at night for 1 to 2 weeks. PEFR reflects the highest rate of expiration, which is demonstrated at the top of the flow-volume loop during the expiratory phase (Fig 12), and represents flow in the large airways of the trachea and larger bronchioles. In normal populations, there is very little decline of the PEFR from evening to morning, whereas in the asthmatic population there is a greater degree of variability. A diurnal PEFR variation of greater than 15%, therefore, is suggestive of asthma.

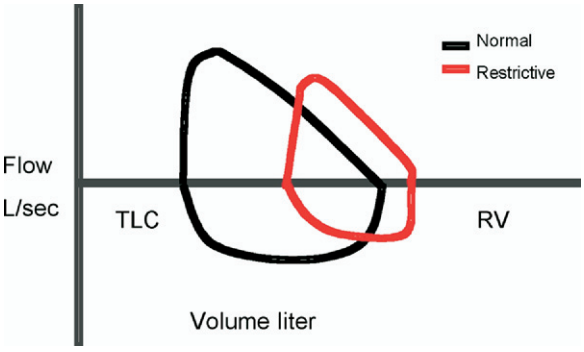

Figure 14 Normal flow-volume loop compared with restrictive flow-volume loop. (TLC, total lung volume; RV, residual volume.)

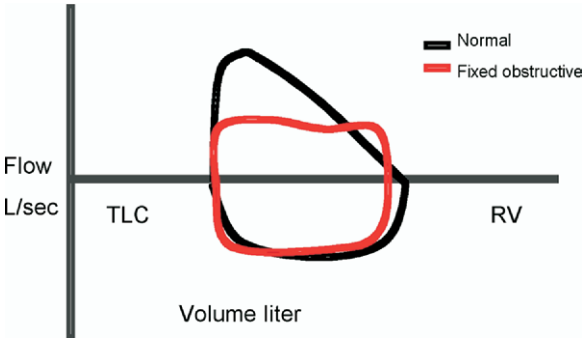

Figure 15 Normal flow-volume loop compared with loop representing fixed obstruction. (TLC, total lung volume; RV, residual volume.)

The flow-volume loop is the other value assessed during FVC. It is measured in relationship of flow (liters/seconds) to volume (liters). The patterns of the flow-volume loop help distinguish between obstructive and restrictive pulmonary disease (Figs 13 and 14). The loop can also help distinguish between different types of obstruction. Variable obstruction (Fig 13) versus fixed obstruction (Fig 15) as in the case of bilateral vocal cord paralyses are different.

Pulmonary testing also includes diffusing capacity, also known as transfer factor, that measures the lung's ability to transfer gas into blood. The gaseous molecule used to measure this index is carbon monoxide. Diffusing capacity (DC) is affected by surface area and thickness of the capillary membrane, volume of blood circulating in capillaries, and the amount of hemoglobin, smoking, altitude, and reaction rate of test gas with hemoglobin.[119] The DC is calculated by the equation:

$$DC = VCO/PACO$$

where DC is diffusion lung capacity, VCO is volume of CO, and PACO is alveolar concentration of CO.

Diffusing capacity can be used to differentiate patients with obstructive disease. For asthmatic patients, the DC is normal while in patients with emphysema, the DC is low.

Body plethysmography, also referred to as a "body box," calculates the functional residual capacity (FRC). Body plethysmography is performed at the end of tidal volume and with the airway occluded. The patient pants against an occluded airway and expands the gas in chest. Then Boyle's law

$$V1P1 = V2P2$$

where V1 is volume one, P1 is pressure one, V2 is volume two, and P2 is pressure two, is used to calculate the functional residual capacity.

FRC can be assessed in patients suspected to have asthma in order to calculate residual volume, which cannot be measured through routine spirometry. To assess residual volume, the functional residual capacity is measured with plethysmography; the expiratory residual volume is then subtracted from the FRC so that the residual volume can be obtained. The residual volume is higher in asthmatic patients due to air trapping.

ASTHMA CONTROL

Patients' often monitor and assess their asthma based only on their symptoms and may be unaware of subtle changes in their health status. Physicians and other health professions often rely primarily on patients' perceptions of their symptoms to monitor asthma and its treatment. This overreliance on symptoms as the primary indicator of the patient's asthma status can lead to an overestimation of the level of asthma control and result in insufficient treatment of the disease, reduced lung function, and limitations in functional ability.[120]

The Concept of Control

Asthma is a disease that affects the patient at any time, day or night; it can impact daily function and activity level or interfere with sleep. The concept of asthma control allows the practitioner to assess patients with asthma with the use of multiple vantage points and thus provide a comprehensive evaluation of their health status. The diagnosis of asthma is based on an assessment of patient symptoms and pulmonary function and is classified according to its severity as outlined in the National Heart, Lung, and Blood Institute (NHLBI) guidelines.[108] The degree of asthma severity refers to the underlying disease process, especially as it is relates to reversibility of lung abnormality, and is used to determine the most appropriate type of treatment for the patient's condition. The severity of the disease is defined as mild, moderate, or severe asthma and as intermittent or persistent.

The concept of asthma control focuses on the adequacy of the treatment rather than the underlying disease state.[121] The primary goals of asthma management are aimed at prevention of troublesome symptoms that occur during the daytime or at night, at prevention of episodes of acute exacerbations, to minimize the use of reliever medications, to maintain active and productive life, and to achieve "near" normal lung function.[122]

Asthma control is a dynamic indicator of the patient's asthma status and provides a means for ongoing assessment. The degree to which an individual perceives one's asthma to be under control is also strongly associated with treatment outcomes for asthma. With strict management guidelines to maximize the control of asthma, individuals are able to not only improve their symptoms but are able to enhance their quality of life significantly as well.[123] This effect is present independent of the severity of asthma.

Assessment of the level of control involves the use of both subjective indexes, such as symptoms and use of reliever medications, along with objective measures of lung function, such as spirometry or peak flow. With a systematic assessment of the patient's level of asthma control, the practitioner can most accurately determine the effectiveness of the current management plan. This allows the physician to best evaluate the relative risks and benefits of the prescribed treatment in relation to desired outcomes of the therapy.

Fluctuations in asthma control. Asthma is characterized by chronic inflammation of the lower respiratory tract. This chronic inflammatory process, modulated by many different cells and chemical mediators, is considered to be the predominant underlying problem for persons with asthma.[124] Symptoms typically associated with this chronic inflammation are wheezing, coughing, chest tightness, and shortness of breath.[108]

The level of control can be influenced by many factors both internal and external to the patient. Fluctuations in asthma control may be attributed to changes in lung function, environmental factors, inadequate medical management, and patient adherence to the prescribed treatment regimen. Reduced lung capacity occurs in individuals with more severe asthma, during respiratory infections, and with bouts of bronchitis, which results in less than optimal asthma control levels. Patients may also experience reduced pulmonary function related to bronchial hyperresponsive, which may occur during the night or in the presence of specific particulates such as smoke or pollens.

Asthma control may also be affected by exposure to certain environmental conditions that occur with air pollution, cigarette or cigar smoke, and chemicals. These particles may exacerbate symptoms in patients who are susceptible to them. Individuals with atopic asthma may also experience fluctuations in level of asthma control and exacerbation of symptoms on exposure to specific allergens. Patients may also experience fluctuations in asthma control as a result of inadequate pharmacotherapeutics or insufficient doses of medication. Finally, asthma control is strongly affected by the patient's level of adherence to the management plan. Patients may be unaware of changes in their asthma status and not recognize the significance of their symptoms. In particular, many individuals have misconceptions about the use of inhaled corticosteroids. Adequate patient education on proper administration of therapies, self-monitoring strategies, and understanding the relative risks and benefits of medications are important components of any teaching plan in order to ensure greater adherence to prescribed therapies.

Assessing Asthma Control

The standard method of assessing control in the person with asthma is through perceptions of the symptoms that are experienced. Individuals monitor such symptoms as their overall shortness of breath, wheezing, and cough as indicators of whether their asthma is adequately controlled. Nocturnal awakenings related to symptoms or waking earlier in the morning are also indications of suboptimal asthma control. Providers also consider frequency of acute episodes of asthma and use of reliever medications as indicators of level of asthma control. It is important to ask patients how often they use their reliever medications on a weekly basis and how often they need to refill this prescription.

A number of studies[125,126] suggest that the reliance on symptoms as the main index of asthma control may be insensitive to early changes in status, and thus result in less-than-optimal control and treatment. In addition, persons who are considered to be "stable" or "well-controlled," based on absence of symptoms, often still experience a greater degree of sleep abnormalities, fatigue, and reduction in functional ability and activity level than matched controls. Several studies[127,128] have also examined patients' perceptions of their asthma severity in relation to objective indexes of pulmonary function. Findings revealed that a high proportion of patients with asthma did not perceive changes in pulmonary function that were detected in simultaneous peak expiratory flow measurements.[128]

The inclusion of an objective measure of lung function, spirometry, or peak flow, is essential in the ongoing assessment of the patient's level of asthma control. Spirometry assesses both inspiratory and expiratory phases of lung function. Responsiveness to administration of bronchodilators in the reversibility of pulmonary restrictions is an important diagnostic finding. Peak flow rates provide a simple and inexpensive measure of maximal lung expiration and can be useful in monitoring the patient's lung status at home or at multiple times during the day. An adequate evaluation of the person with asthma uses both subjective and objective indexes in order to fully appreciate the current health status.

Measures of Asthma Control

The importance of an adequate assessment of asthma control for clinical and research application has been the catalyst in the development of several questionnaires. These instruments are designed to capture the multidimensionality of asthma. The development of reliable, validated questionnaires of asthma control provides practitioners with standardized measures to assess the patient. In general, these tools assess multiple aspects of control over a specified period of time. A time period of between 8 and 15 days has been deemed sufficient for evaluating level of asthma control, however, some measures assess the patient's status over a longer period of time.[129]

Asthma Therapy Assessment Questionnaire (ATAQ). The ATAQ was designed to evaluate the multidimensionality of asthma control and to identify potential barriers in the adequate management of the disease. The ATAQ is a brief, self-administered questionnaire in which patients reflect on their level of asthma control over the previous 4 weeks.[130-132] The 4 areas or dimensions assessed by the questionnaire are: 1) nocturnal awakenings related to asthma symptoms; 2) interference with normal daily activities such as missed time from work or school; 3) use of reliever inhaler medications; and 4) self-perception of asthma control.[131,132]

The patient response to each of the 4 dimensions is scored dichotomously as either having a control problem (1 = 1 control problem) or not having a problem (0 = no control problem). The scores on the 4 areas are summed and provide an index that ranges from 0 (no control problems) to 4 (4 control problems).[130,131] The ATAQ was compared to both generic and disease-specific quality of life indexes in a sample of 5181 adult asthma patients from a large health maintenance organization. The 4 dimensions of asthma control, assessed by the ATAQ, were found to correlate strongly with the SF-36 scale, a generic quality of life index and 2 asthma-specific quality of life measures, the standardized version of the Asthma Quality of Life Questionnaire (AQLQ) and the Mini (AQLQ).[131]

Asthma Control Question (ACQ). The ACQ assesses perceptions of the adequacy of asthma control in adults. The tool was designed to measure asthma control along a continuum ranging from well-controlled to extremely poorly controlled.[121,133] The questionnaire asks patients to recall their symptoms and use of short acting β_2-agonist medication during the past week. Respondents indicate their asthmatic symptoms related to 7 points: 1) how often they were woken by asthma during the night; 2) how bad were asthma symptoms on awakening in the morning; 3) how limited were activities because of asthma; 4) how much shortness of breath was experienced; and 5) how much time did they wheeze. In addition to assessing symptoms, a sixth question concerns the person's use of short-acting β_2-agonist. And the seventh point is lung function measured by the clinic staff grading the FEV_1 % predicted.

Each of the 7 questions is scored on a 7-point scale; 0 indicates good control and a score of 6 indicates poor control. The overall score for the ACQ is computed as the mean of the 7 responses. Reliability of the ACQ, estimated as within-subject variance related to total variance and known as the intraclass correlation coefficient (ICC), was very good with an ICC = 0.90. The ability of the ACQ to detect changes in asthma control was very good with a responsive index of 1.06 ($P < 0.001$).[121,133]

Asthma Control Test (ACT). The ACT is a 5-item assessment tool to identify patients with poorly controlled asthma. This test is designed to quantify the level of asthma control with or without an assessment of lung function. The ACT is easily administered in the office setting and the instrument is accessible through the internet (http://www.asthmaactionamerica.org/i_have_asthma/control_

test.html). Respondents rate their degree of asthma control during the past 4 weeks on the following 5 questions: 1) How much of the time did your asthma keep you from getting as much done at work or home? 2) How often have you had shortness of breath? 3) How often did your asthma symptoms wake you up at night or earlier than usual in the morning? 4) How often have you used rescue inhaler? and 5) How would you rate your asthma control?

The ACT has demonstrated good internal consistency reliability ($r = 0.84$). In order to validate the asthma control as measure by the ACT, scores on the test were correlated with both FEV_1 values and specialist ratings of control. ACT scores were found to moderately correlate with specialist's ratings of control ($r = 0.45$), although correlations with FEV_1 values were low ($r = 0.19$).[120] The ACT can be a valuable patient-based tool to assess asthma control in the office setting. The test is available in both pediatric and adult versions.

There are several areas of concern related to assessing levels of asthma control in patients. At this time, there is still a lack of consensus among health professionals in the definition and interpretation of the various levels of control. There are also limitations in the use of standardized measures including time constraints when administering within practice settings as well as scoring tests in a way that is meaningful to both patient and provider. It is important to recognize that disease severity can also significantly affect level of asthma control and must be considered in the evaluation process.

Predicting Asthma Control

Combescure et al[129] sought to demonstrate the complementary relationship between the severity of asthma and level of asthma control over time. With the use of a predictive model, they followed patients prospectively over a 3-year period to evaluate transitions in health states related to their asthma. The sample consisted of 365 adults with persistent asthma of varying severity levels who had been diagnosed on the basis of the criteria of the American Thoracic Society for less than 1 year. Patients received treatment for their asthma in accord with guideline recommendations.

Asthma control level was chosen as the health state to be studied over time. An asthma control level was allocated to each patient enrolled in the study based on episodes of exacerbations, β_2-agonist used associated with symptoms, measured FEV_1 value, and dyspnea during the previous month. Based on this assessment, patients were designated to be in optimal control, suboptimal control, or unacceptable control. Patients were treated and then followed over time to determine transitions in their health state related to this level of asthma control.

Patients with mild-moderate persistent asthma demonstrated a high probability of transition from a suboptimal or unacceptable state of control to optimal level of control with treatment. In these individuals, the suboptimal state was not considered a natural end-state but rather as an unstable transition state. Patients with mild-moderate persistent disease responded quickly to treatment and were able to transition much more rapidly from an unacceptable state to an optimal state compared with individuals with more severe asthma.

In contrast, patients with severe persistent asthma had a high probability of transitioning to an unacceptable level of control and remaining in this unacceptable state despite treatment. When transitions to a more optimal state did occur, they tended to take more time than those with less severe disease. In this study, the severity of asthma did influence the patient's ability to transition to a more optimal level of control during treatment.

Table 6
Asthma-related parameters used by physicians to assess control

Parameter	Percent of patients
B_2-agonist use	>80
Cough	>65
Wheezing	>65
Shortness of breath	~65
Limitations in physical activity	~60
Nighttime awakenings	~60
PEF	~18
FEV_1	~10

Boulet LP, Phillips R, O'Byrne PO, et al. Evaluation of asthma control by physicians and patients: Comparison with current guidelines. Can Respir J 2002;9:417–23.

Evaluation of Asthma Control

A study by Boulet et al[134] identified parameters used by physicians to determine patients' asthma control compared with recommended guideline criteria and patient perceptions of control. A total of 183 Canadian physicians evaluated 856 adult and pediatric patients with mild to moderately severe asthma, who were considered as uncontrolled according to the current asthma guidelines. The physician composition consisted of general practitioners (73.8%), allergists and pulmonologists (14.2%), and pediatricians (12%). Although these patients' asthma statuses would not be considered under control based on guideline criteria, a majority (66.2%) of the patients and almost half (43.3%) the physicians rated symptoms as being adequately controlled.

The asthma-related parameter most frequently identified by physicians to assess asthma control was use of short-acting β_2-agonists, which was used to evaluate more than 80% of patients. Physicians identified cough and wheezing as the second most frequently used parameter, which was used in over 65% of patients. Shortness of breath, limitations in activities, and nighttime awakenings were also used in evaluating asthma control in 60% of patients (Table 6). Objective measures of lung function were used very infrequently; PEF was assessed in only 18% of patients and FEV_1 values obtained in 10% of patients.[134]

Analysis on a subgroup of physicians who were allergists and pulmonologists demonstrated that they often included

Table 7
Levels of asthma control

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less weekly)	More than twice weekly	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever or rescue treatment	None (twice or less weekly)	More than twice weekly	
Lung function (PEF or FEV_1)	Normal	<80% predicted or of personal best PEF	
Exacerbations	None	One or more yearly	One in any week

Any exacerbation should prompt review or maintenance treatment to ensure that it is adequate. By definition, an exacerbation in any week makes that an uncontrolled asthma week. Lung function is not a reliable test for children 5 years and younger. Adapted from GINA Guidelines. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention 2006. Available at www.ginasthma.org.

lung function measures as part of their evaluation of asthma control. Overall, these specialists obtained FEV_1 values in 61% of patients and PEF rates in 48% of patients. The majority of physicians in this study based their assessment of asthma control on clinical symptoms and use of reliever medications. Objective measures of airflow obstruction and pulmonary function were rarely performed by the general practitioners.[134]

Quantifying Asthma Control

Some physicians have tried to quantify the level of asthma control based on specific criteria. Boulet et al[135] developed the Asthma Control Scoring System for quantifying control. The Asthma Control Scoring System provides percentages on 3 criteria, symptom score, physiological assessment (FEV_1 or PEF), and an inflammatory assessment (sputum eosinophil count). Based on this scoring system, significant correlations were found between patient self-evaluations of control and asthma symptom score. However, there were no significant correlations between mean scores for symptoms, expiratory flow values, and airway inflammation measures. Patient self-reported symptoms also did not correlate with objective measures of lung function. Similar findings were reported by other researchers who noted that alterations in physical functioning and general health status related to reduced pulmonary function may occur even though changes in respiratory status are not perceived by the person.[125,126,128]

Guidelines-Based Asthma Control

The 2006 Global Initiative for Asthma (GINA) guidelines[136] present a series of management strategies for asthma that are based on control rather than on treatment of disease severity. Older management systems, such as those outlined by the NAEPP, have traditionally based asthma treatment on the assessment of severity and chronicity of disease. The 2006 GINA guidelines suggest that control is a more active index of the patient's current asthma status and reflects an evaluation of the patient's current physical status and their response to treatment. In order to apply a graduated approach to medical management, GINA outlines a specific set of objective criteria for assessment of asthma control. These criteria are shown in Table 7.

Elements of control described in the 2006 GINA approach include daytime symptoms, limitation of activities, nocturnal symptoms and nocturnal awakenings, the use of rescue medications, and assessment of lung function with either peak expiratory flow or spirometry. In addition, the occurrence of asthma exacerbations is a central criterion to assess control under this system. The goal of optimal control is for the patient to experience no symptoms, either at night or during the day, and to have no limitation in activities. Symptoms that require use of rescue medications should not occur more frequently than twice weekly. In addition, asthma exacerbations should occur less than annually. Any deviation from these baseline measures demonstrate that asthma is becoming poorly controlled and requires a reevaluation and assessment of controller medication strategy.[136]

Conclusions

In assessing level of asthma control, both practitioners and patients tend to use global assessment measures. Patients focus primarily on control of their asthma symptoms, feelings of well being, and their functional ability. Practitioners rely predominately on the presence of asthma-related symptoms and the overuse of reliever medications to determine whether the patient is being adequately controlled. Based on their assessment methods, both practitioners and patients tend to overestimate the adequacy of asthma control, which may result in insufficient treatment of the disease and a state of suboptimal control.[120] In order to obtain a more complete

Table 8
Key components of the patient-doctor partnership

- Education.
- Joint setting of goals.
- Self-monitoring. The person with asthma is taught to combine assessment of asthma control with educated interpretation of key symptoms.
- Regular review of asthma control, treatment, and skills by a health care professional.
- Written action plan. The person with asthma is taught which medications to use regularly and which to use as needed, and how to adjust treatment in response to worsening asthma control.
- Self-monitoring is integrated with written guidelines for both the long-term treamtent of asthma and the treatment of asthma exacerbations.

Adapted from GINA Guidelines. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention 2006. Available at www.ginasthma.org.

assessment of the patients' asthma control level and adequately manage the disease, the otolaryngologist should adopt an approach that incorporates both subjective information and an objective measure of lung function. Several standardized questionnaires are available to assess asthma control in the office setting. An asthma control measure coupled with a pulmonary function test will provide the physician with a thorough assessment profile in order to better manage the patient with asthma and achieve optimal control.

ASTHMA MANAGEMENT

As noted above, current trends in the management of the patient with asthma suggest that therapeutic interventions and strategies should be based on an assessment of the current level of the patient's asthma control, rather than on the severity of the patient's disease at presentation as evaluated by pulmonary function.[136] Control reflects a more dynamic index of the patient's current functional status and can be more readily evaluated and managed. Active treatment for the patient's asthma can be initiated and updated more easily with this approach than through the use of a static concept of disease severity. Guidelines such as those presented in the 2006 GINA document therefore stress a control-based strategy for management of the asthmatic patient.[136]

In addition, management of the patient with asthma requires an ongoing partnership between the physician, the patient, and the patient's family in order to achieve optimal levels of control and patient function. Such an approach involves not only the manipulation of pharmacologic therapies, but also demands a dynamic strategy to bring asthma under the best possible levels of control. Components of this partnership are noted in Table 8 and demonstrate that treat-

Table 9
Effectiveness of avoidance in certain indoor allergens

Measure	Evidence of effect on allergen levels	Evidence of clinical benefit
House dust mites		
Encase bedding	Some	None (adults) Some (children)
Wash bedding in hot water	Some	None
Replace carpet with hard flooring	Some	None
Use acaracides and/or tannic acid	Weak	None
Minimize dust-collecting objects	None	None
Vacuum with HEPA vacuum cleaners	Weak	None
Remove, hot wash, freeze plush toys	None	None
Pets		
Remove cat/dog from the home	Weak	None
Keep pet from living area and bedrooms	Weak	None
Use HEPA-filter air cleaners	Some	None
Wash pet	Weak	None
Replace carpet with hard flooring	None	None
Vacuum with HEPA vacuum cleaners	None	None

Adapted from GINA Guidelines. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention 2006. Available at www.ginasthma.org.

ment of asthma involves continued, ongoing evaluation and collaboration.

Measures to prevent the development of asthma, to lessen the acute and chronic symptoms of asthma, and to slow the progression of disease should be a hallmark of asthma management. These measures must include the avoidance and reduction of exposure to risk factors and triggers and should be used whenever possible. Although the limitation of tobacco exposure during and after pregnancy has been shown to have benefit in reducing childhood development of asthma,[137] there have been no other environmental interventions that have been adequately demonstrated to prevent the development of asthma.

Exacerbations of asthma can be caused by a wide variety of factors, including allergens, viral infections, pollutants or irritants, and medications. Common indoor allergens that are associated with the development and expression of asthma include house dust mites, pets, cockroaches, and fungi/mold.[8] Evidence that a reduction of environmental exposure to single antigens will lead to clinical benefit for the patient is, unfortunately, scanty (Table 9).[136] Combined, targeted multiallergen reduction studies have not yet been conducted and are indicated as targets for future research.

Avoidance methods for outdoor allergens are often difficult and impractical to implement. Because outdoor allergens in most climates are usually present only on a seasonal basis, an awareness of seasonal triggers can assist the patient and family in managing outdoor activities during times of high pollen load. Outdoor chemical pollutants are also known to aggravate asthma symptoms. Particulate materials in the air, as well as levels of irritant chemicals such as ozone, are associated with an increase in symptoms and exacerbations of asthma.[138]

As discussed earlier, rhinitis and acute or chronic rhinosinusitis are significant comorbid diseases that are associated with asthma. Exacerbations of these illnesses will make asthma more symptomatic and difficult to control. In addition, gastroesophageal reflux is a significant comorbid condition that may also increase asthma symptoms, especially in children.[139] When asthma is difficult to bring under adequate control, the clinician must evaluate whether any of these concurrent illnesses may need to be addressed.

Heart disease can also contribute to breathlessness in patients and can significantly compromise pulmonary function.[140] Patients treated with medications that provide beta-agonist blockade may experience increases in airway hyperresponsiveness, smooth muscle contraction with bronchoconstriction, and exacerbation of their asthma symptoms. Obesity and increased body-mass index (BMI) can also be associated with increased expression of asthma symptoms.[141] Weight reduction should be encouraged in patients with asthma and is associated with improvement in asthma symptom control. Finally, although asthma is not a psychosomatic illness, as was postulated in the past, psychological stress can be associated with symptom exacerbations.[142]

Pharmacologic Therapy

Medications that are used to treat asthma can be classified as either controllers or relievers. Controller medications are used by patients on a daily basis to maintain asthma under stable clinical control. They are used to modify the underlying airway inflammation that is central to the pathophysiology of asthma and provide benefit primarily via their anti-inflammatory effects. Controller medications for asthma include inhaled corticosteroids, leukotriene modifiers, mast cell-stabilizing medications, sustained-release theophylline, and, as a last resort, systemic corticosteroids. In addition, β2-agonists are used as adjuncts for asthma control but should not be used without anti-inflammatory medications because of their potential risk with use as monotherapy for asthma.[143] Reliever medications are designed to be used only on an "as-needed" basis to quickly reverse bronchoconstriction and its clinical consequences. These reliever medications include rapid-acting β2-agonists, rapid-acting inhaled anticholinergics, and less commonly, short-acting theophylline or short-acting oral β2-agonists.

Corticosteroids. Inhaled corticosteroids are the most effective current class of asthma controller therapy. Their mechanism of action involves the down-regulation of airway inflammation and results in improved clinical control. Inhaled corticosteroids have demonstrated efficacy in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyperresponsiveness, reducing frequency and severity of exacerbations, and reducing asthma mortality. Despite their clinical efficacy, inhaled corticosteroids do not provide a cure for asthma; a significant minority of asthma patients may have a suboptimal response to inhaled corticosteroid therapy. Inhaled corticosteroids differ in their potency and systemic bioavailability. Their dosage can be titrated to affect the desired level of response, yet to lessen the occurrence of undesired adverse effects. The understanding and flexible use of controller treatment options, both alone and in combination, are critical components of asthma management strategies used by clinicians.

Local adverse effects from the use of inhaled corticosteroids include oropharyngeal candidiasis and dysphonia, hoarseness, and coughing from upper airway irritation. When metered-dose inhalers (MDIs) are used for drug administration, the incidence of these local effects may be reduced through the use of spacers. Mouth washing after oral inhalation may also reduce the risk of oral candidiasis. In addition, the use of pro-drugs that are activated in the lungs but not in the pharynx (eg, ciclesonide) and new formulations and delivery devices that reduce oropharyngeal deposition may minimize local oral effects.

Inhaled corticosteroids are absorbed from the lung and therefore are systemically bioavailable to varying degrees. The risk of systemic effects from an inhaled corticosteroid depends on the drug's dose and potency, the frequency of use, the delivery system, the systemic bioavailability of the molecule, the extent of first-pass hepatic metabolism to inactive metabolites, and the half-life of the fraction of drug

systemically absorbed. The systemic effects of these medications, therefore, differ among the various inhaled corticosteroids. Comparative studies have generally demonstrated that ciclesonide, budesonide, mometasone furoate, and fluticasone propionate at equipotent doses have less systemic effect than older agents such as triamcinalone acetonide.[144]

The systemic side-effects of long-term treatment with high doses of inhaled corticosteroids include skin bruising, hypothalamic-pituitary-adrenal axis (HPA) suppression, and decreased bone mineral density. Inhaled corticosteroids are associated with ocular abnormalities, including cataracts and glaucoma in cross-sectional studies, but prospective studies have not demonstrated evidence of posterior-subcapsular cataracts. Studies that attempt to investigate the role of inhaled corticosteroids in the development of adverse systemic effects are often confounded by the concurrent use of oral corticosteroids by patients with severe asthma.

Though differences exist among the various inhaled corticosteroids, treatment with low doses of these agents on a daily basis is not generally associated with significant suppression of the HPA axis in children. At higher doses, however, mild changes in HPA axis function can be demonstrated in some individuals.[145] The clinical relevance of these findings is not known. Low doses of inhaled corticosteroids used chronically throughout childhood do not appear to affect final adult height.[146] At higher doses, however, children and adolescents do appear to demonstrate some dose-related susceptibility to systemic growth effects with inhaled corticosteroids.[147]

In patients who experience significant exacerbations of asthma and in those patients who require aggressive therapy to bring their asthma under control, systemic treatment with corticosteroids is sometimes necessary. These medications are potent anti-inflammatory agents and demonstrate good efficacy in decreasing the symptoms of asthma and bringing that disease under better control. Systemic corticosteroids are associated with a higher incidence of adverse effects, with these effects dependent on length of therapy and dosage. Current treatment strategies recommend that parenteral deposition preparations of corticosteroids (eg, Depo-Medrol) should not be used due to their risk of adverse effects, irreversibility once administered, and difficulty in dosage titration. Oral regimens with agents such as prednisone are preferred.[3]

Leukotriene modifiers. Leukotriene modifiers have also demonstrated benefit in the treatment of asthma. These medications include 2 classes of medications: cysteinyl leukotriene (CysLT) receptor antagonists (montelukast, pranlukast, and zafirlukast) and a 5-OH-lipoxygenase inhibitor (zileuton). Clinical studies in patients with asthma have demonstrated that leukotriene modifiers demonstrate some effect on bronchodilatation and can reduce symptoms including cough.[148] Leukotriene-modifying medications can also improve lung function through their reduction in airway inflammation and can decrease the frequency of asthma exacerbations.[149] These medications can be used as alternative treatments for patients with mild persistent asthma and are efficacious in some patients with aspirin-sensitive asthma. When used alone as controller medications, however, the effects of leukotriene modifiers have generally been observed to be less than that of low doses of inhaled corticosteroids.[150] In patients who require inhaled corticosteroids for asthma control, leukotriene modifiers are not considered as appropriate alternatives unless reduction of inflammatory control is desired. Leukotriene modifiers used as add-on therapy, however, may reduce the dose of inhaled corticosteroids among patients with moderate to severe asthma and may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled corticosteroids. The additive effects of these agents are less pronounced than those of long-acting β2-agonists when used adjuvantly with inhaled corticosteroids.[151]

β2-agonists. Long-acting β2-agonists, including agents such as salmeterol and formoterol, have been used as adjuvant treatments for asthmatic patients with significant bronchospasm. These medications do not decrease inflammation among patients with asthma, however, and therefore should not be used as monotherapy in asthma management.[137] Addition of long-acting β2-agonists to a daily regimen of inhaled corticosteroids has been shown to improve asthma symptom scores.[152] In addition, these agents used in combination with inhaled corticosteroids can decrease nocturnal asthma, improve lung function, decrease the need for rapid-acting inhaled β2-agonists, and reduce the number of asthma exacerbations.[152] Combination therapy, therefore, can often achieve better clinical control of asthma and at lower doses of inhaled corticosteroids than through the use of inhaled corticosteroids alone. Because of the concern raised by recent research, combination therapy may be indicated primarily for the treatment of asthma among patients not controlled on inhaled corticosteroids alone.[136] Data that indicate a possible increased risk of asthma-related deaths associated with the use of salmeterol[143] led to advisories from the U. S. Food and Drug Administration (FDA) and Health Canada that long-acting β2-agonists are not a substitute for first-line anti-inflammatory therapy and should only be used in combination with an appropriate dose of an inhaled corticosteroid as determined by a physician. Caution should therefore be exercised in the use of long-acting β2-agonists as a component of the treatment regimen in patients with asthma.

The regular use of β2-agonists in both short- and long-acting forms may lead to tachyphylaxis and refractoriness to β2-agonists.[153] The increased need for rescue therapy with short-acting β2-agonists such as albuterol is a strong clinical indication that the patient's asthma control is declining and that intervention is necessary to stabilize the asthma. Frequent use of these agents, especially exceeding 3 times daily, can be associated with significant tachyphylaxis and death.[154] Patients must be advised that symptoms that require more frequent use of these medications should be

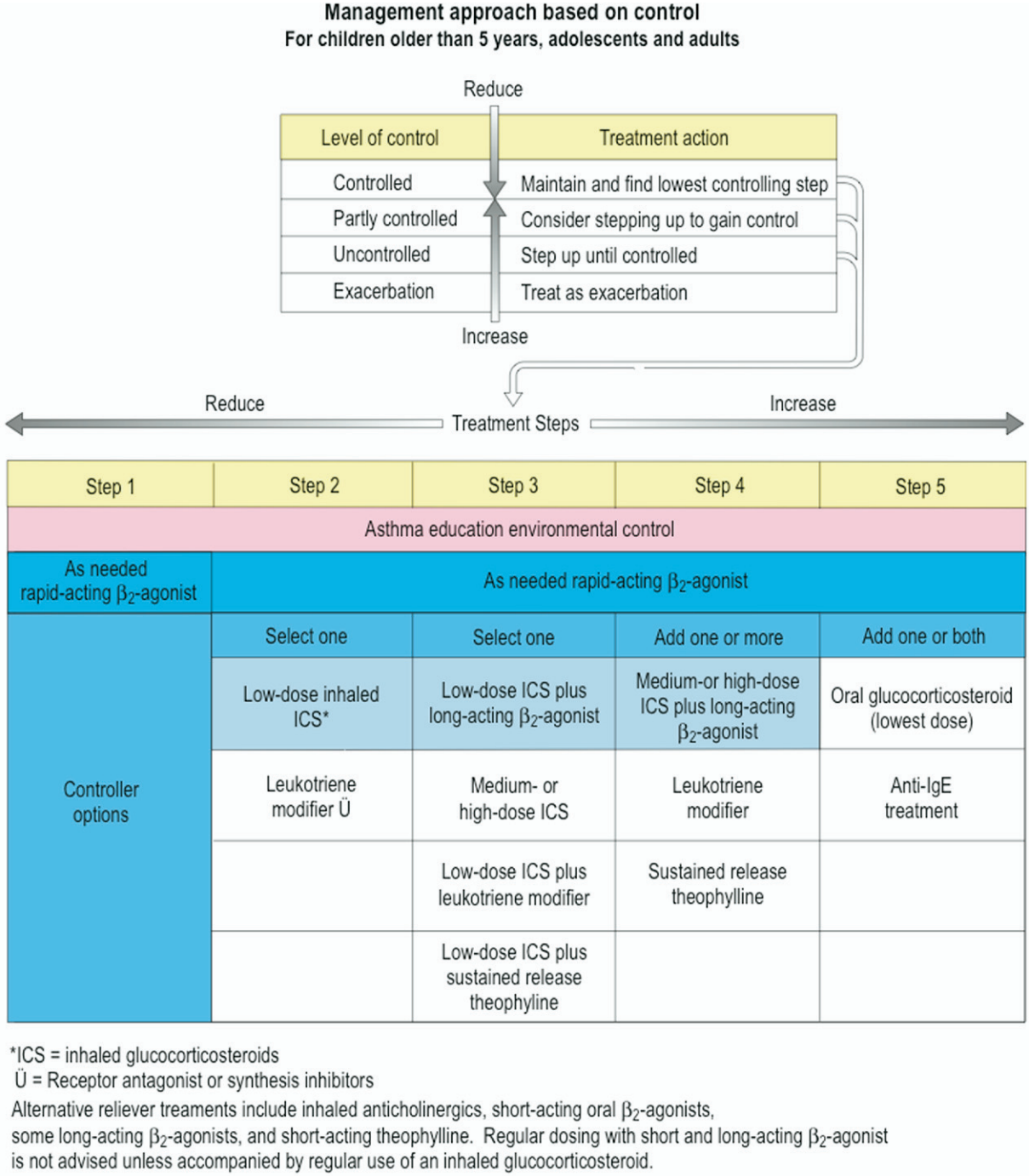

Figure 16 Control-based asthma management algorithm. Adapted from GINA Guidelines. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention 2006. Available at www.ginasthma.org.

reported to their clinicians immediately so that their pulmonary and functional status can be evaluated and appropriately managed.

Theophylline. Another agent that had been used more frequently in the past for the management of the patient with asthma is theophylline. Theophylline acts primarily as a bronchodilator but also demonstrates some modest anti-inflammatory properties.[155] It is available in sustained-release formulations that are suitable for once- or twice-daily dosing. Data on the relative clinical efficacy of theophylline as a long-term controller medication, however, are lacking. Available evidence does suggest that sustained-release theophylline has little benefit as a first-line controller medication. It may be effective as an add-on therapy in patients who do not demonstrate control on inhaled corticosteroids alone. The sudden withdrawal of sustained-release theophylline has been asso-

ciated with the deterioration of asthma control and significant exacerbation of symptoms.[156]

An algorithm for asthma management based on control, based on principles drawn from the 2006 GINA guidelines, is shown in Figure 16.[136] It is first essential to bring the patient's asthma under adequate control, with the use of treatment based on the severity of patient's symptoms and functional impairment. Once asthma control has been achieved, ongoing monitoring of symptoms and patient function is essential to maintain adequate control and to maximize function and quality of life. A step-care approach to management is based on an assessment of the patient's current level of control and is used to establish the lowest dose and intensity of treatment necessary to maintain control. This regimen must also consider an approach that minimizes the cost and maximizes the safety of treatment. Asthma is a dynamic and fluctuant disease, and treatment must be monitored and adjusted periodically based on indexes of loss of control, such as the expression of worsening symptoms, the accelerating use of short acting bronchodilators, or the development of asthma exacerbations.

In general, current research suggests that any patient with persistent asthma should be treated with anti-inflammatory therapy. As indicated in the GINA guidelines, milder levels of disease can be treated with either a low-dose inhaled corticosteroid or an oral leukotriene modifier. As patient symptoms worsen and control deteriorates, medical therapy should intensify through either an increase in the dose of inhaled corticosteroid medications, the addition of a long-acting bronchodilator, or both. In significant exacerbations of asthma and with marked deterioration in the level of control, short courses of oral corticosteroids may be necessary to achieve rapid improvement in symptoms and pulmonary function and to bring exacerbations under maximal control. As control is achieved, the intensity of medical management can be modified appropriately and lower levels of medication can be used.

Asthma control must be monitored jointly by the health care professional, the patient, and the family at regular intervals, and can use either an observational approach or a validated composite measure of control. The frequency of health care visits are based on the patient's initial level of clinical severity, as well as consideration of the patient's ability to actively monitor control of his or her asthma. Patients are typically seen monthly at first, with quarterly visits common once control has been achieved. After an acute exacerbation, the patient should be seen within 2 weeks in order to evaluate response to therapy and adjust treatment accordingly.

Conclusion

The use of guidelines-based management approaches in the treatment of the patient with asthma can be effective in allowing patients to achieve maximal levels of function with few adverse effects. Current strategies stress that asthma treatment should be guided by the adequacy of asthma control and should use anti-inflammatory medications for all patients with persistent asthma. Use of rescue medications should be infrequent, and patients should have little or no interference with sleep and daytime activities. These management approaches also stress flexibility in application of various therapeutic strategies and ongoing evaluation of the patient with asthma to achieve maximum levels of control.

CONCLUSIONS

Asthma is a chronic inflammatory disease of the lower airways that continues to increase in prevalence around the world. It reflects a regional process that is representative of a larger inflammatory condition of the respiratory system that involves the respiratory mucosa of the upper and lower airways. Common pathophysiologic processes influence this respiratory system so that diseases that affect the nose and sinuses will often affect the lungs and bronchi at the same time. In addition, individuals who develop symptoms isolated to one portion of this common respiratory system are at significantly greater risk of developing disease in other parts of this system over time.

Otolaryngologists are familiar with inflammatory diseases of the upper airway such as rhinitis and rhinosinusitis and manage patients with these common conditions on a daily basis. It is clear, however, that otolaryngologists, as well as other specialty and primary care physicians, may not be aware that lower respiratory diseases such as asthma are common among patients with nasal and sinus diseases. Both epidemiologic and pathophysiologic data support the increased prevalence of asthma among patients with rhinitis and rhinosinusitis. Increased awareness of the possible presence of asthma among these patients will allow physicians who treat upper airway disease to recognize, diagnose, and manage patients with asthma.

Physicians who actively manage patients with allergic diseases need to increase their vigilance in screening and assessing those patients for lower airway symptoms. They need to be aware of symptoms that suggest a potential diagnosis of asthma and conduct appropriate screening studies to evaluate the presence of this disease. The use of physical examination data and pulmonary function testing are effective to assist with this diagnostic strategy and to identify patients who might benefit from asthma management.

In addition, physicians should be familiar with clinical strategies and treatment methods that are effective in the management of patients with various degrees of asthmatic disease. Otolaryngologists and other physicians possess skills in diagnosis and assessment that will allow them to evaluate patients for asthma and can easily broaden their skill sets to manage patients with asthma should they choose to do so. Collaboration with pulmonary specialists and with otolaryngologists, pediatricians, and internal medicine physicians who specialize in the practice of allergy will allow partnerships to develop to further refine and optimize asthma treatment when appropriate. Ongoing assessment of patient response to therapy and level of asthma control will allow the physician to maximize treatment benefit and patient function.[39]

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