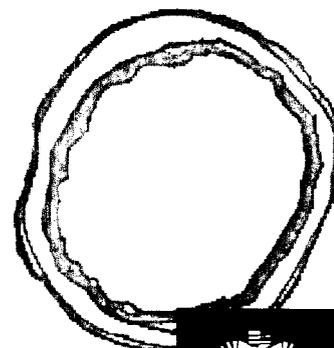
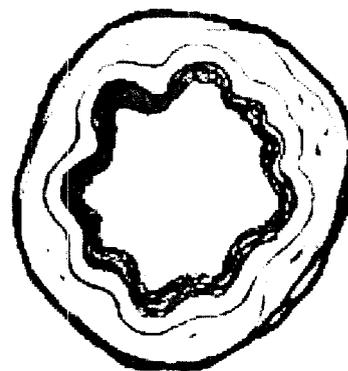
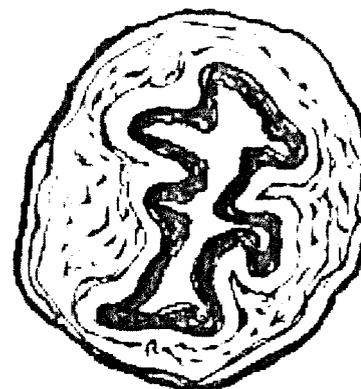
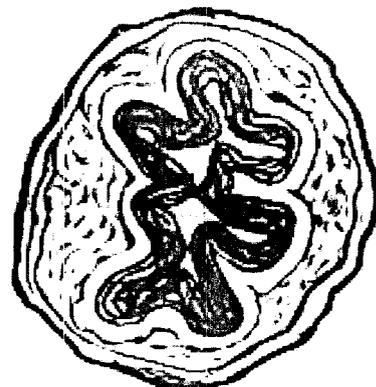


CLINICAL PRACTICE GUIDELINES

EXPERT PANEL REPORT 2

Guidelines for the Diagnosis and Management of Asthma



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GUIDELINES

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Diagnosis and
Management
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and Blood Institute*

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P R E F A C E

In 1991, under the auspices of the National Asthma Education and Prevention Program (NAEPP), the first Expert Panel on the Management of Asthma published *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma*. This landmark report redefined commonly held beliefs about asthma care, thus setting the stage for nationwide improvements in the clinical management of asthma and stimulating a variety of novel research. An enormous amount of work has been done since the release of the report to deepen our understanding of the pathogenesis of asthma and increase our knowledge about effective approaches to asthma diagnosis, monitoring, pharmacologic and environmental management, and patient education. Accordingly, the decision was made to update and revise the 1991 report to identify progress made over the last 6 years.

Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (EPR-2) is the culmination of more than 3 years of preparatory analysis, meetings, and writing and review cycles involving many individuals, not the least of whom were the members of the second Expert Panel. Under the able leadership of Dr. Shirley Murphy, Panel chair, the second Expert Panel diligently met its charge of producing an accurate, up-to-date source of information for clinicians on asthma diagnosis and management. Panel members conducted their work not only with skill and a depth of clinical and academic knowledge, but also with a commitment to quality and an impressive spirit of collaboration. The National Heart, Lung, and Blood Institute and the organizations that comprise the NAEPP Coordinating Committee sincerely appreciate the work of Dr. Murphy, the Expert Panel, and all others who participated in the preparation of this report.

The task before us is to explore innovative methods to broadly disseminate and encourage implementation of these updated asthma care recommendations. The first steps will be to adapt the EPR-2 into formats that meet the needs of various health professionals and then to disseminate these materials. However, these national-level efforts will have an impact on asthma care only if they occur in concert with local activities to encourage use of EPR-2 materials. Ultimately, broad change in clinical practice depends on the influence of local physicians and other health professionals who not only provide state-of-the-art care to their patients, but also communicate to their peers the importance of doing the same. We are optimistic that over the next several years, the joint efforts of the NAEPP, its Coordinating Committee member organizations, and committed professionals at the local level will result in extensive implementation of the recommendations in the EPR-2. We ask for the assistance of every reader in reaching our ultimate goal: improving asthma care and the quality of life for every patient with asthma and their families.

Publications from the National Asthma Education and Prevention Program can be ordered through the National Heart, Lung, and Blood Institute Information Center, P.O. Box 30105, Bethesda, MD 20824-0105. Publications are also available through the Internet at <http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm>.



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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. In the United States, asthma affects 14 million to 15 million persons. It is the most common chronic disease of childhood, affecting an estimated 4.8 million children (Adams and Marano 1995; Centers for Disease Control and Prevention 1995). People with asthma collectively have more than 100 million days of restricted activity and 470,000 hospitalizations annually. More than 5,000 people die of asthma annually. Asthma hospitalization rates have been highest among blacks and children, while death rates for asthma were consistently highest among blacks aged 15 to 24 years (Centers for Disease Control and Prevention 1996). These rates have increased or remained stable over the past decade. This report describes the appropriate use of the available therapies in the management of asthma.

To help health care professionals bridge the gap between current knowledge and practice, the National Heart, Lung, and Blood Institute's (NHLBI) National Asthma Education and Prevention Program (NAEPP) has convened two Expert Panels to prepare guidelines for the diagnosis and management of asthma. The NAEPP Coordinating Committee, under the leadership of Claude Lenfant, M.D., director of the NHLBI, convened the first Expert Panel in 1989. The charge to this Panel was to develop a report that would provide a general approach to diagnosing and managing asthma based on current science. The *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma* (NAEPP 1991) was published in 1991, and the recommendations for the treatment of asthma were organized around four components of effective asthma management:

- Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy

- Environmental control measures to avoid or eliminate factors that precipitate asthma symptoms or exacerbations
- Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma as well as pharmacologic therapy to manage asthma exacerbations
- Patient education that fosters a partnership among the patient, his or her family, and clinicians

The principles addressed within these four components of asthma management served as the starting point for the development of two additional reports prepared by asthma experts from many countries in cooperation with the NHLBI: the *International Consensus Report on Diagnosis and Management of Asthma* (NHLBI 1992) and the *Global Initiative for Asthma* (NHLBI/WHO 1995). The *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2) is the latest report from the National Asthma Education and Prevention Program and updates the 1991 Expert Panel Report. The second Expert Panel critically reviewed and built upon the reports listed above.

This report presents basic recommendations for the diagnosis and management of asthma that will help clinicians and patients make appropriate decisions about asthma care. Of course, the clinician and patient need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. The NAEPP, and all who participated in the development of this latest report, hope that the patient with asthma will be the beneficiary of the recommendations in this document. This report is not an official regulatory document of any Government agency.

METHODS USED TO DEVELOP THIS REPORT

The NAEPP Coordinating Committee established a Science Base Committee of U.S. asthma experts who began work in early 1994 to monitor the scientific literature and advise the Coordinating Committee when an update of the 1991 *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma* was needed. The Science Base Committee, along with international members of the Global Initiative for Asthma, examined all the relevant literature on asthma in human subjects published in English between 1991 and mid-1995, obtained through a series of MEDLINE database searches. More than 5,000 abstracts were reviewed. In 1995, the Science Base Committee recommended to the NAEPP Coordinating Committee that sufficient new information had been published since 1991 to convene a panel of experts to update the first Expert Panel Report.

The second Expert Panel is a multidisciplinary group of clinicians and scientists with expertise in asthma management. The Panel includes health professionals in the areas of general medicine, family practice, pediatrics, emergency medicine, allergy, pulmonary medicine, nursing, pharmacy, and health education. Among the Panel members are individuals who served on either the Science Base Committee or the 1991 Expert Panel. Other members were chosen based on names submitted by NAEPP Coordinating Committee member organizations. Several Expert Panel members are themselves members of the Coordinating Committee. Representatives from several Federal agencies also have participated.

The charge to the Panel was to prepare recommendations for use by clinicians working in diverse health care settings that address the practical decisionmaking issues in the diagnosis and management of asthma. The Panel also was requested to develop specific aids to facilitate implementation of the recommendations.

Panel members were asked to base their recommendations on their review of the scientific literature and to cite studies that support the recommendations. When a clear recommendation could not be extracted from the studies (e.g., studies were not available, were conflicting, or

were equivocal), the Panel was asked to label the recommendation as "based on the opinion of the Expert Panel," "recommended by the Expert Panel," or similar terminology. When a whole section was "based on the opinion of the Expert Panel," this was indicated at the beginning of the section (e.g., see component 1-Initial Assessment and Diagnosis).

This report was prepared in a systematic and iterative process. In addition to the Science Base Committee review of the scientific literature, the Panel conducted in-depth reviews of the literature in selected areas it considered controversial. In interpreting the literature, the Panel considered the nature and quality of the study designs and analyses. Given the complexities of several issues, the Panel chose not to use the strict evidence ranking system used in the guidelines development procedures of the U.S. Preventive Services Task Force. However, this procedure was applied in the area of peak flow monitoring. The Panel submitted their interpretation of the literature and related recommendations for multiple reviews by their fellow Expert Panel members and outside reviewers.

The development of EPR-2 was directed by an Executive Committee; each member of the Executive Committee headed a subcommittee assigned to prepare a specific chapter. Each member of the Panel was assigned to one of the subcommittees. The subcommittees were responsible for reviewing the pertinent literature and drafting the recommendations with the supporting evidence for the full Panel to review. Once the subcommittee reports were prepared, the full Panel critically reviewed the evidence and rationale for each recommendation, discussed revisions, and reached final agreement on each recommendation. A vote was taken to confirm the consensus of the Panel. The final report was approved by the NAEPP Coordinating Committee via mail. Box 1 summarizes the draft, review, and consensus-building process.

The development of this report was *entirely* funded by the National Heart, Lung, and Blood Institute, National Institutes of Health. Panel members and reviewers participated as volunteers and were compensated only for travel expenses related to the two Expert Panel meetings and the Executive Committee meetings.

BOX 1. MAJOR EVENTS IN THE DEVELOPMENT OF EPR-2

First Expert Panel meeting	June 1995
Executive Committee meeting	November 1995
Executive Committee meeting (by phone)	February 1996
Second Expert Panel meeting and review by outside experts	May 1996
Review by NAEPP Coordinating Committee member organizations	August 1996
Executive Committee meeting	October 1996
Mail Review, Expert Panel	December 1996
Mail Review and Approval, NAEPP Coordinating Committee	January 1997

The goal of the *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* is to serve as a comprehensive guide to diagnosing and managing asthma. Implementation of EPR-2 recommendations is likely to increase some costs of asthma care by increasing the number of primary care visits for asthma and the use of asthma medications, environmental control products and services, and equipment (e.g., spacer/holding chamber devices). However, asthma diagnosis and management are expected to improve, which should reduce the numbers of lost school and work days, hospitalizations and emergency department visits, and deaths due to asthma. A net reduction in total health care costs should result. The NAEPP encourages research to evaluate the impact of implementing the recommendations in this report.

OVERVIEW OF THE REPORT

Each section of EPR-2 begins with a list of "Key Points" and "Differences From 1991 Expert Panel Report." A brief overview of each section is provided below.

Pathogenesis and Definition

In the 1991 Expert Panel Report, the role of inflammation in the pathogenesis of asthma was emphasized although the scientific evidence for the involvement of inflammation in asthma was just emerging. Now in 1997, although the role of inflammation is still evolving as a concept, a much firmer scientific basis exists to indicate that asthma results from complex interactions among inflammatory cells, mediators, and the cells and tissues resident in the airways.

Thus, asthma is now defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

COMPONENT 1: Measures of Assessment and Monitoring

Initial Assessment and Diagnosis of Asthma

Making the correct diagnosis of asthma is extremely important. Clinical judgment is required because signs and symptoms vary widely from patient to patient as well as within each patient over time. To establish the diagnosis of asthma, the clinician must determine that:

- Episodic symptoms of airflow obstruction are present.
- Airflow obstruction is at least partially reversible.
- Alternative diagnoses are excluded.

This section differs from the 1991 Expert Panel Report in several ways. Asthma severity classifications have been changed from mild, moderate, and severe to mild intermittent, mild persistent, moderate persistent, and severe persistent to more accurately reflect the clinical manifestations of

asthma. The Panel emphasizes that patients at any level of severity can have mild, moderate, or severe exacerbations. In addition, information on wheezing in infancy and vocal cord dysfunction has been expanded in the differential diagnosis section in component 1. Situations that may warrant referral to an asthma specialist have been refined with input from specialty and primary care physicians.

Periodic Assessment and Monitoring

To establish whether the goals of asthma therapy have been achieved, ongoing monitoring and periodic assessment are needed. The goals of asthma therapy are to:

- Prevent chronic and troublesome symptoms
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

Several types of monitoring are recommended: signs and symptoms, pulmonary function, quality of life/functional status, history of asthma exacerbations, pharmacotherapy, and patient-provider communication and patient satisfaction.

The Panel recommends that patients, especially those with moderate-to-severe persistent asthma or a history of severe exacerbations, be given a written action plan based on signs and symptoms and/or peak expiratory flow. As in the 1991 report, daily peak flow monitoring is recommended for patients with moderate-to-severe persistent asthma. In addition, the Panel states that any patient who develops severe exacerbations may benefit from peak flow monitoring. A complete review of the literature on peak flow monitoring was conducted, evidence tables were prepared, and the results of this analysis are summarized in the report.

COMPONENT 2: Control of Factors Contributing to Asthma Severity

Exposure of sensitive patients to inhalant allergens has been shown to increase airway inflammation, airway hyperresponsiveness, asthma symptoms, need for medication, and death due to asthma. Substantially reducing exposures significantly reduces these outcomes. Environmental tobacco smoke is a major precipitant of asthma symptoms in children, increases symptoms and the need for medications, and reduces lung function in adults. Increased air pollution levels of respirable particulates, ozone, SO₂, and NO₂ have been reported to precipitate asthma symptoms and increase emergency department visits and hospitalizations for asthma. Other factors that can contribute to asthma severity include rhinitis and sinusitis, gastroesophageal reflux, some medications, and viral respiratory infections. EPR-2 discusses environmental control and other measures to reduce the effects of these factors.

COMPONENT 3: Pharmacologic Therapy

EPR-2 offers an extensive discussion of the pharmacologic management of patients at all levels of asthma severity. It is noted that asthma pharmacotherapy should be instituted in conjunction with environmental control measures that reduce exposure to factors known to increase the patient's asthma symptoms.

As in the 1991 report, a stepwise approach to pharmacologic therapy is recommended, with the type and amount of medication dictated by asthma severity. EPR-2 continues to emphasize that persistent asthma requires daily long-term therapy in addition to appropriate medications to manage asthma exacerbations. To clarify this concept, the EPR-2 now categorizes medications into two general classes: *long-term-control medications* to achieve and maintain control of persistent asthma and *quick-relief medications* to treat symptoms and exacerbations.

Observations into the basic mechanisms of asthma have had a tremendous influence on therapy. Because inflammation is considered an early and persistent component of asthma, therapy for persistent asthma must be directed toward long-term

suppression of the inflammation. Thus, EPR-2 continues to emphasize that the most effective medications for long-term control are those shown to have anti-inflammatory effects. For example, early intervention with inhaled corticosteroids can improve asthma control and normalize lung function, and preliminary studies suggest that it may prevent irreversible airway injury.

An important addition to EPR-2 is a discussion of the management of asthma in infants and young children that incorporates recent studies on wheezing in early childhood. Another addition is discussions of long-term-control medications that have become available since 1991—long-acting inhaled beta₂-agonists, nedocromil, zafirlukast, and zileuton.

Recommendations for managing asthma exacerbations are similar to those in the 1991 Expert Panel Report. However, the treatment recommendations are now on a much firmer scientific basis because of the number of studies addressing the treatment of asthma exacerbations in children and adults in the past 6 years.

COMPONENT 4: Education for a Partnership in Asthma Care

As in the 1991 Expert Panel Report, education for an active partnership with patients remains the cornerstone of asthma management and should be carried out by health care providers delivering asthma care. Education should start at the time of asthma diagnosis and be integrated into every step of clinical asthma care. Asthma self-management education should be tailored to the needs of each patient, maintaining a sensitivity to cultural beliefs and practices. New emphasis is placed on evaluating outcomes in terms of patient perceptions of improvement, especially quality of life and the ability to engage in usual activities. Health care providers need to systematically teach and frequently review with patients how to manage and control their asthma. Patients also should be provided with and taught to use a written daily self-management plan and an action plan for exacerbations. It is especially important to give a written action plan to patients with moderate-to-severe persistent asthma or a history of severe exacerbations. Appropriate patients should also receive a daily asthma diary. Adherence should be encouraged by promoting open communication;

individualizing, reviewing, and adjusting plans as needed; emphasizing goals and outcomes; and encouraging family involvement.

In summary, the 1997 *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* reflects the experience of the past 6 years as well as the increasing scientific base of published articles on asthma. The Expert Panel hopes this new report will assist the clinician in forming a valuable partnership with patients to achieve excellent asthma control and outcomes.

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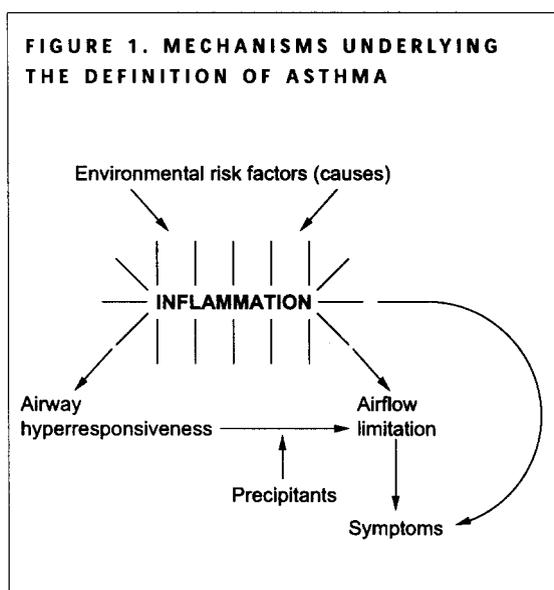
PATHOGENESIS AND DEFINITION

KEY POINTS

- Asthma, whatever the severity, is a chronic inflammatory disorder of the airways. This has implications for the diagnosis, management, and potential prevention of the disease.
- The immunohistopathologic features of asthma include:
 - Denudation of airway epithelium
 - Collagen deposition beneath basement membrane
 - Edema
 - Mast cell activation
 - Inflammatory cell infiltration
 - Neutrophils (especially in sudden-onset, fatal asthma exacerbations)
 - Eosinophils
 - Lymphocytes (TH2-like cells)
- Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.
- Airway inflammation also contributes to several forms of airflow limitation, including acute bronchoconstriction, airway edema, mucus plug formation, and airway wall remodeling. These features lead to bronchial obstruction.
- Atopy, the genetic predisposition for the development of an IgE-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma.

DIFFERENCES FROM 1991 EXPERT PANEL REPORT

- The critical role of inflammation in asthma has been further substantiated by research. It is recognized that asthma results from complex interactions among inflammatory cells, mediators, and other cells and tissues resident in the airway.
 - Evidence indicates that subbasement membrane fibrosis may occur in some patients and that these changes contribute to persistent abnormalities in lung function. The importance of airway remodeling and the development of persistent airflow limitation need further exploration and may have significant implications for the treatment of asthma.
-



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The clinician, physiologist, immunologist, and pathologist all may have different perspectives on asthma based on their individual viewpoints and experience. The merging of these different perspectives into an acceptable definition of asthma has begun to occur and is important for more specific and effective treatment of this disease and for investigation into its pathogenesis. Furthermore, even though this disorder affects virtually the entire spectrum of life, asthma has certain age-specific characteristics and differential diagnosis issues that need to be considered in both its treatment and its etiology.

Based on current knowledge, a working definition of asthma is: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli (NHLBI 1995). Moreover, recent evidence indicates that subbasement membrane fibrosis may occur in some patients with asthma and that these changes contribute to persistent abnormalities in lung function (Roche 1991).*

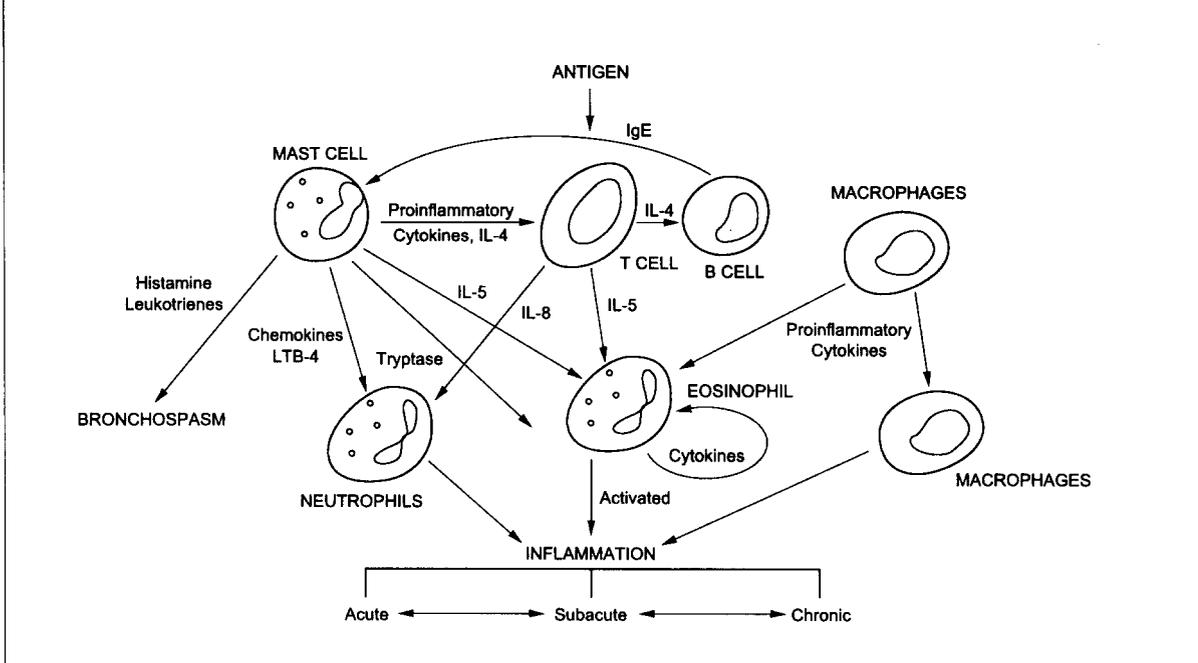
This working definition and its expanded recognition of key features of asthma have been derived from studying how airway changes in asthma relate to various factors associated with the development of allergic inflammation (e.g., allergens, respiratory viruses, and some occupational exposures, as illustrated in figure 1). From this approach has come a more comprehensive understanding of asthma pathogenesis, the development of persistent airway inflammation, and the profound implications these issues have for the diagnosis, treatment, and potential prevention of asthma.

AIRWAY PATHOLOGY AND ASTHMA

Until recently, information on airway pathology in asthma has come largely from post-mortem examination (Dunnill 1960), which shows that both large and small airways often contain plugs composed of mucus, serum proteins, inflammatory cells, and cellular debris. Viewed microscopically, airways are infiltrated with eosinophils and mononuclear cells, and there is vasodilation and evidence of microvascular leakage and epithelial disruption. The airway smooth muscle is often hypertrophied, which is characterized by new vessel formation, increased numbers of epithelial goblet cells, and deposition of interstitial collagens beneath the epithelium. These features of airway wall remodeling further underscore the importance of chronic, recurrent inflammation in asthma and its effects on the airway. Moreover, these morphologic changes may not be completely reversible. Consequently, research is currently focused on determining whether these changes can be prevented or modified by early diagnosis, avoidance of factors that contribute to asthma severity, and pharmacologic therapy directed at suppressing airway inflammation.

Establishing the relationship between the pathologic changes and the clinical features of asthma has been difficult. Fiberoptic bronchoscopy with lavage and biopsy provide new insight into mechanisms of airway disease and features that link altered lung function to a specific type of mucosal inflammation (Laitinen et al. 1985; Beasley et al. 1989; Jeffery et al. 1989). From such studies, evidence has emerged that mast cells, eosinophils, epithelial cells, macrophages, and activated T cells are key features of the inflammatory process of asthma (Djukanovic et al. 1990), as illustrated in figure 2. These cells can influence airway function through secretion of preformed and newly synthe-

FIGURE 2. CELLULAR MECHANISMS INVOLVED IN AIRWAY INFLAMMATION



sized mediators that act either directly on the airway or indirectly through neural mechanisms (Emanuel and Howarth 1995). Furthermore, with the use of cellular and molecular biological techniques, subpopulations of T lymphocytes (TH2) have been identified as important cells that may regulate allergic inflammation in the airway through the release of selective cytokines and also establish disease chronicity (Robinson et al. 1992). In addition, constituent cells of the airway, including fibroblasts, endothelial cells, and epithelial cells, also contribute to this process by releasing cytokines and chemokines.

The above factors may be important in both initiating and maintaining the level of airway inflammation (Robinson et al. 1993). It is hypothesized that airway inflammation can be acute, subacute, and chronic. The acute inflammatory response is represented by the early recruitment of cells to the airway. In the subacute phase, recruited and resident cells are activated to cause a more persistent pattern of inflammation. Chronic inflammation is characterized by a persistent level of cell damage and an ongoing repair process, changes that may cause permanent abnormalities in the airway.

Finally, it is recognized that specific adhesion proteins, found in the vascular tissue, lung matrix, and bronchial epithelium, may be critical in directing and anchoring cells in the airway, thus causing the inflammatory changes noted (Albelda 1991). From these studies of the histological features associated with asthma has come evidence of an association between airway inflammation and markers of airway disease severity and an indication that this process is multicellular, redundant, and self-amplifying.

Cell-derived mediators can influence airway smooth muscle tone, modulate vascular permeability, activate neurons, stimulate mucus secretion, and produce characteristic structural changes in the airway (Horwitz and Busse 1995). These mediators can target ciliated airway epithelium to cause injury or disruption. As a consequence, epithelial cells and myofibroblasts—present beneath the epithelium—proliferate and begin to deposit interstitial collagens in the lamina reticularis of the basement membrane. This may explain apparent basement membrane thickening and the irreversible airway changes that may occur in some asthma patients (Roche 1991). Other changes, including hypertrophy and hyperplasia of airway smooth muscle, increases in goblet cell number, enlargement of submucous glands, and remodeling of the airway connective tissue, are

components of asthma that need to be recognized in both its pathogenesis and treatment. This inflammatory process is redundant in its ability to alter airway physiology and architecture.

Child-Onset Asthma

Asthma often begins in childhood, and when it does, it is frequently found in association with atopy, which is the genetic susceptibility to produce IgE directed toward common environmental allergens, including house-dust mites, animal proteins, and fungi (Larsen 1992). With the production of IgE antibodies, mast cells and possibly other airway cells (e.g., lymphocytes) are sensitized and become activated when they encounter specific antigens. Although atopy has been found in 30 to 50 percent of the general population, it is frequently found in the absence of asthma. Nevertheless, atopy is one of the strongest predisposing factors in the development of asthma (Sporik et al. 1990). Furthermore, among infants and young children who have wheezing with viral infections, allergy or family history of allergy is the factor that is most strongly associated with continuing asthma through childhood (Martinez et al. 1995).

Adult-Onset Asthma

Although asthma begins most frequently in childhood and adolescence, it can develop at anytime in life. Adult-onset asthma can occur in a variety of situations. In adult-onset asthma, allergens may continue to play an important role. However, in some adults who develop asthma, IgE antibodies to allergens or a family history of asthma are not detected. These individuals often have coexisting sinusitis, nasal polyps, and sensitivity to aspirin or related nonsteroidal anti-inflammatory drugs. The mechanisms of nonallergic, or intrinsic, asthma are less well established, although the inflammatory process is similar (but not identical) to that seen in atopic asthma (Walker et al. 1992).

Occupational exposure to workplace materials (animal products; biological enzymes; plastic resin; wood dusts, particularly cedar; and metals) (see component 2) can cause airway inflammation, bronchial hyperresponsiveness, and clinical signs of asthma (Chan-Yeung and Malo 1994; Fabbri et al. 1994). Identification of the causative agent and its removal from the workplace can reduce symptoms; however, some individuals will have persistent asthma even though exposure to the causative

agent is eliminated. The mechanisms of this form of asthma are not clearly established.

RELATIONSHIP OF AIRWAY INFLAMMATION AND LUNG FUNCTION

Airway Hyperresponsiveness

An important feature of asthma is an exaggerated bronchoconstrictor response to a wide variety of stimuli. The propensity for airways to narrow too easily and too much is a major, but not necessarily unique, feature of asthma. Airway hyperresponsiveness leads to clinical symptoms of wheezing and dyspnea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Research indicates that airway hyperresponsiveness is important in the pathogenesis of asthma and that the level of airway responsiveness usually correlates with the clinical severity of asthma.

Airway hyperresponsiveness can be measured by inhalation challenge testing with methacholine or histamine, as well as after exposure to such non-pharmacologic stimuli as hyperventilation with cold dry air, inhalation of hypotonic or hypertonic aerosols, or after exercise (O'Connor et al. 1989). In addition, variability between morning and evening peak expiratory flow (PEF) appears to reflect airway hyperresponsiveness and may serve as a measure of airway hyperresponsiveness, asthma instability, or asthma severity.

The factors contributing to airway inflammation in asthma are multiple and involve a variety of different inflammatory cells (as illustrated in figure 2) (Busse et al. 1993). It is also apparent that asthma is not caused by either a single cell or a single inflammatory mediator but rather results from complex interactions among inflammatory cells, mediators, and other cells and tissues resident in airways. An initial trigger in asthma may be the release of inflammatory mediators from bronchial mast cells, macrophages, T lymphocytes, and epithelial cells. These substances direct the migration and activation of other inflammatory cells, such as eosinophils and neutrophils, to the airway where they cause injury, such as alterations in epithelial integrity, abnormalities in autonomic neural control of airway tone, mucus hypersecretion, change in mucociliary function, and increased airway smooth muscle responsiveness.

The importance of the airway inflammatory response to airway hyperresponsiveness is substantiated by several observations. First, airway markers of inflammation correlate with bronchial hyperresponsiveness. Second, treatment of asthma and modification of airway inflammatory markers not only reduce symptoms but also diminish airway responsiveness. However, the relationship between airway inflammation and airway responsiveness is complex. Some investigations have shown that although anti-inflammatory therapy reduced airway hyperresponsiveness, it did not eradicate it. A small study found that control of airway inflammation did not control bronchial hyperresponsiveness (Lundgren et al. 1988). Thus, factors in addition to inflammation may contribute to airway hyperresponsiveness.

Airflow Obstruction

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

- **Acute bronchoconstriction.** Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from the mast cell that include histamine, tryptase, leukotrienes, and prostaglandins (Marshall and Bienenstock 1994), which directly contract airway smooth muscle. Aspirin and other nonsteroidal anti-inflammatory drugs (see component 2) can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE-dependent response also involves mediator release from airway cells (Fischer et al. 1994). In addition, other stimuli, including exercise, cold air, and irritants, can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation (Busse et al. 1993). There is emerging evidence that stress can play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of proinflammatory cytokines (Friedman et al. 1994).
- **Airway edema.** Airway wall edema, even without smooth muscle contraction or bronchoconstriction, limits airflow in asthma. Increased microvascular permeability and leakage caused by released mediators also contribute to mucosal thickening and

swelling of the airway. As a consequence, swelling of the airway wall causes the airway to become more rigid and interferes with airflow.

- **Chronic mucus plug formation.** In severe intractable asthma, airflow limitation is often persistent. In part, this change may arise as a consequence of mucus secretion and the formation of inspissated mucus plugs.
- **Airway remodeling.** In some patients with asthma, airflow limitation may be only partially reversible. The etiology of this component is not as well studied as other features of asthma but may relate to structural changes in the airway matrix that may accompany longstanding and severe airway inflammation. There is evidence that a histological feature of asthma in some patients is an alteration in the amount and composition of the extracellular matrix in the airway wall (Djukanovic et al. 1990; Laitinen and Laitinen 1994). As a consequence of these changes, airway obstruction may be persistent and not responsive to treatment. Regulation of this repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response. Although yet to be fully explored, the importance of airway remodeling and the development of persistent airflow limitation suggest a rationale for early intervention with anti-inflammatory therapy.

RELEVANCE OF CHRONIC AIRWAY INFLAMMATION TO ASTHMA THERAPY

Although inflammation can be used to describe a variety of conditions in various diseases, the inflammatory response in asthma has special features that include eosinophil infiltration, mast cell degranulation, interstitial airway wall injury, and lymphocyte activation. Furthermore, there is evidence that a TH2 lymphocyte cytokine profile (i.e., IL-4 and IL-5) is instrumental in initiating and sustaining the inflammatory process (James and Kay 1995; Ricci et al. 1993) (see figure 2). These observations also have become important in directing treatment in asthma. It is hypothesized that inflammation is an early and persistent component of asthma. As a consequence, therapy to suppress the inflammation must be long term. Furthermore, preliminary evidence suggests that early intervention with anti-inflam-

matory therapy may modify the disease process (Agertoft and Pedersen 1994; Laitinen et al. 1992; Djukanovic et al. 1992).

Observations into the basic mechanisms of asthma have had tremendous impact and influence on therapy. Studies have shown that improvements in asthma control achieved with high doses of inhaled corticosteroids are associated with improvement in markers of airway inflammation (Laitinen et al. 1992; Djukanovic et al. 1992). These observations indicate that a strong link may exist between features of airway inflammation, bronchial hyperresponsiveness, and asthma symptoms and severity. Furthermore, insight into the mechanisms of asthma with airway inflammation and bronchial wall repair has become a driving factor in designing logical, and hopefully effective, treatment paradigms.

Another area that needs clarification is the classification of compounds as anti-inflammatory in nature. Because many factors contribute to the inflammatory response in asthma, many drugs may fit this category. At present, corticosteroids are the anti-inflammatory compounds that have been demonstrated to modify histopathological features of asthma (Barnes 1995). It may be necessary to evaluate each new compound for the specificity of its "anti-inflammatory" action and determine from appropriate observations whether the compound is indeed anti-inflammatory and what consequences this has on the clinical features of the disease.

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COMPONENT 1 : **MEASURES OF ASSESSMENT AND MONITORING**

Initial Assessment and Diagnosis of Asthma

KEY POINTS

- To establish a diagnosis of asthma, the clinician should determine that:
 - Episodic symptoms of airflow obstruction are present.
 - Airflow obstruction is at least partially reversible.
 - Alternative diagnoses are excluded.
- Recommended mechanisms to establish the diagnosis are:
 - Detailed medical history
 - Physical exam focusing on the upper respiratory tract, chest, and skin
 - Spirometry to demonstrate reversibility
- Additional studies may be considered to:
 - Evaluate alternative diagnoses
 - Identify precipitating factors
 - Assess severity
 - Investigate potential complications
- Recommendations are presented for referral for consultation or care to a specialist in asthma care.

DIFFERENCES FROM 1991 EXPERT PANEL REPORT

- Severity classifications were changed from mild, moderate, and severe to mild intermittent, mild persistent, moderate persistent, and severe persistent.
 - Examples of questions to use for diagnosis and initial assessment of asthma were added.
 - Information on wheezing in infancy and vocal cord dysfunction was expanded in the differential diagnosis section.
 - Criteria for referral were refined with input from specialty and primary care physicians.
 - More specific recommendations for measuring peak expiratory flow (PEF) diurnal variation are made.
-

The guidelines to help establish a diagnosis of asthma presented in this component are based on the opinion of the Expert Panel.

The clinician trying to establish a diagnosis of asthma should determine that:

- Episodic symptoms of airflow obstruction are present.
- Airflow obstruction is at least partially reversible.
- Alternative diagnoses are excluded.

A careful medical history, physical examination, pulmonary function tests, and additional tests will provide the information needed to ensure a correct diagnosis of asthma (see box 1). Each of these methods of assessment is described in this section.

Clinical judgment is needed in conducting the assessment for asthma. Patients with asthma are heterogeneous and present signs and symptoms that vary widely from patient to patient as well as within each patient over time.

BOX 1. KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF ASTHMA

Consider asthma and performing spirometry if any of these indicators are present.* These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of asthma. Spirometry is needed to establish a diagnosis of asthma.

- Wheezing—high-pitched whistling sounds when breathing out—especially in children. (Lack of wheezing and a normal chest examination do not exclude asthma.)
- History of any of the following:
 - Cough, worse particularly at night
 - Recurrent wheeze
 - Recurrent difficulty in breathing
 - Recurrent chest tightness
- Reversible airflow limitation and diurnal variation as measured by using a peak flow meter, for example:
 - Peak expiratory flow (PEF) varies 20 percent or more from PEF measurement on arising in the morning (before taking an inhaled short-acting beta₂-agonist) to PEF measurement in the early afternoon (after taking an inhaled short-acting beta₂-agonist).
- Symptoms occur or worsen in the presence of:
 - Exercise
 - Viral infection
 - Animals with fur or feathers
 - House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
 - Mold
 - Smoke (tobacco, wood)
 - Pollen
 - Changes in weather
 - Strong emotional expression (laughing or crying hard)
 - Airborne chemicals or dusts
 - Menses
- Symptoms occur or worsen at night, awakening the patient.

*Eczema, hay fever, or a family history of asthma or atopic diseases are often associated with asthma, but they are not key indicators.

MEDICAL HISTORY

A detailed medical history of the new patient known or thought to have asthma should address the items listed in figure 1-1. The medical history can help:

- *Identify the symptoms likely to be due to asthma.*
See figure 1-2 for sample questions.
- *Support the likelihood of asthma* (e.g., patterns of symptoms, family history of asthma or allergies).
- *Assess the severity of asthma* (e.g., symptom frequency and severity, exercise tolerance, hospitalizations, current medications). See figure 1-3 for a description of the levels of asthma severity.
- *Identify possible precipitating factors* (e.g., viral respiratory infections; exposure at home, work, day care, or school to inhalant allergens or irritants such as tobacco smoke). See component 2, Control of Factors Contributing to Asthma Severity, for more details.

PHYSICAL EXAMINATION

The upper respiratory tract, chest, and skin are the focus of the physical examination for asthma. Physical findings that increase the probability of asthma include:

- *Hyperexpansion of the thorax*, especially in children; use of accessory muscles; appearance of hunched shoulders; and chest deformity.
- *Sounds of wheezing during normal breathing, or a prolonged phase of forced exhalation* (typical of airflow obstruction). Wheezing during forced exhalation is not a reliable indicator of airflow limitation. In mild intermittent asthma, or between exacerbations, wheezing may be absent.
- *Increased nasal secretion, mucosal swelling, and nasal polyps.*
- *Atopic dermatitis/eczema* or any other manifestation of an allergic skin condition.

PULMONARY FUNCTION TESTING (SPIROMETRY)

Spirometry measurements (FEV_1 , FVC, FEV_1/FVC) before and after the patient inhales a short-acting bronchodilator should be undertaken for patients in whom the diagnosis of asthma is being considered (Bye et al. 1992; Li and O'Connell 1996). This helps determine whether there is airflow obstruction and whether it is reversible over the short term (see box 2 for further information). Spirometry is generally valuable in children over age 4; however, some children cannot conduct the maneuver adequately until after age 7.

Spirometry typically measures the maximal volume of air forcibly exhaled from the point of maximal inhalation (forced vital capacity, FVC) and the volume of air exhaled during the first second of the FVC (forced expiratory volume in 1 second, FEV_1). Airflow obstruction is indicated by reduced FEV_1 and FEV_1/FVC values relative to reference or predicted values. Significant reversibility is indicated by an increase of >12 percent and 200 mL in FEV_1 after inhaling a short-acting bronchodilator (American Thoracic Society 1991) (see figure 1-4 for example of a spirometric curve for this test). A 2- to 3-week trial of oral corticosteroid therapy may be required to demonstrate reversibility. The spirometry measures that establish reversibility may not indicate the patient's best lung function.

Abnormalities of lung function are categorized as restrictive and obstructive defects. A reduced ratio of FEV_1/FVC (i.e., <65 percent) indicates obstruction to the flow of air from the lungs, whereas a reduced FVC with a normal FEV_1/FVC ratio suggests a restrictive pattern. The severity of abnormality of spirometric measurements is evaluated by comparison of the patient's results with reference values based on age, height, sex, and race (American Thoracic Society 1991).

Although asthma is typically associated with an obstructive impairment that is reversible, neither this finding nor any other single test or measure is adequate to diagnose asthma. Many diseases are associated with this pattern of abnormality. The patient's pattern of symptoms (along with other information from the patient's medical history) and exclusion of other possible diagnoses also are needed to establish a diagnosis of asthma. In severe cases, the FVC may also be reduced, due to trapping of air in the lungs.

FIGURE 1-1. SUGGESTED ITEMS FOR MEDICAL HISTORY*

A detailed medical history of the new patient who is known or thought to have asthma should address the following items:

1. **Symptoms**
 - Cough
 - Wheezing
 - Shortness of breath
 - Chest tightness
 - Sputum production
2. **Pattern of symptoms**
 - Perennial, seasonal, or both
 - Continual, episodic, or both
 - Onset, duration, frequency (number of days or nights, per week or month)
 - Diurnal variations, especially nocturnal and on awakening in early morning
3. **Precipitating and/or aggravating factors**
 - Viral respiratory infections
 - Environmental allergens, indoor (e.g., mold, house-dust mite, cockroach, animal dander or secretory products) and outdoor (e.g., pollen)
 - Exercise
 - Occupational chemicals or allergens
 - Environmental change (e.g., moving to new home; going on vacation; and/or alterations in workplace, work processes, or materials used)
 - Irritants (e.g., tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases, and aerosols)
 - Emotional expressions (e.g., fear, anger, frustration, hard crying or laughing)
 - Drugs (e.g., aspirin; beta-blockers, including eye drops; nonsteroidal anti-inflammatory drugs; others)
 - Food, food additives, and preservatives (e.g., sulfites)
 - Changes in weather, exposure to cold air
 - Endocrine factors (e.g., menses, pregnancy, thyroid disease)
4. **Development of disease and treatment**
 - Age of onset and diagnosis
 - History of early-life injury to airways (e.g., bronchopulmonary dysplasia, pneumonia, parental smoking)
 - Progress of disease (better or worse)
 - Present management and response, including plans for managing exacerbations
 - Need for oral corticosteroids and frequency of use
 - Comorbid conditions
5. **Family history**
 - History of asthma, allergy, sinusitis, rhinitis, or nasal polyps in close relatives
6. **Social history**
 - Characteristics of home including age, location, cooling and heating system, wood-burning stove, humidifier, carpeting over concrete, presence of molds or mildew, characteristics of rooms where patient spends time (e.g., bedroom and living room with attention to bedding, floor covering, stuffed furniture)
 - Smoking (patient and others in home or day care)
 - Day care, workplace, and school characteristics that may interfere with adherence
 - Social factors that interfere with adherence, such as substance abuse
 - Social support/social networks
 - Level of education completed
 - Employment (if employed, characteristics of work environment)
7. **Profile of typical exacerbation**
 - Usual prodromal signs and symptoms
 - Usual patterns and management (what works?)
8. **Impact of asthma on patient and family**
 - Episodes of unscheduled care (emergency department, urgent care, hospitalization)
 - Life-threatening exacerbations (e.g., intubation, intensive care unit admission)
 - Number of days missed from school/work
 - Limitation of activity, especially sports and strenuous work
 - History of nocturnal awakening
 - Effect on growth, development, behavior, school or work performance, and lifestyle
 - Impact on family routines, activities, or dynamics
 - Economic impact
9. **Assessment of patient's and family's perceptions of disease**
 - Patient, parental, and spouse's or partner's knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment
 - Patient perception and beliefs regarding use and long-term effects of medications
 - Ability of patient and parents, spouse, or partner to cope with disease
 - Level of family support and patient's and parents', spouse's, or partner's capacity to recognize severity of an exacerbation
 - Economic resources
 - Sociocultural beliefs

*This list does not represent a standardized assessment or diagnostic instrument. The validity and reliability of this list have not been assessed.

FIGURE 1-2. SAMPLE QUESTIONS* FOR THE DIAGNOSIS AND INITIAL ASSESSMENT OF ASTHMA

A "yes" answer to any question suggests that an asthma diagnosis is likely.

In the past 12 months, . . .

- Have you had a sudden severe episode or recurrent episodes of coughing, wheezing (high-pitched whistling sounds when breathing out), or shortness of breath?
- Have you had colds that "go to the chest" or take more than 10 days to get over?
- Have you had coughing, wheezing, or shortness of breath during a particular season or time of the year?
- Have you had coughing, wheezing, or shortness of breath in certain places or when exposed to certain things (e.g., animals, tobacco smoke, perfumes)?
- Have you used any medications that help you breathe better? How often?
- Are your symptoms relieved when the medications are used?

In the past 4 weeks, have you had coughing, wheezing, or shortness of breath . . .

- At night that has awakened you?
- In the early morning?
- After running, moderate exercise, or other physical activity?

*These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

Office-based physicians who care for asthma patients should have access to spirometry, which is useful in both diagnosis and periodic monitoring. Spirometry should be performed using equipment and techniques that meet standards developed by the American Thoracic Society (1995). Correct technique, calibration methods, and maintenance of equipment are necessary to achieve consistently accurate test results. Maximal patient effort in performing the test is required to avoid important errors in diagnosis and management.

Training courses in the performance of spirometry that are approved by the National Institute for Occupational Safety and Health are available (800-35NIOSH). When office spirometry shows severe abnormalities, or if questions arise regarding test accuracy or interpretation, the Expert Panel recommends further assessment in a specialized pulmonary function laboratory.

ADDITIONAL STUDIES

Even though additional studies are not routine, they may be considered. No one test or set of tests is appropriate for every patient. However, the following procedures may be useful when considering alternative diagnoses, identifying precipitating factors, assessing severity, and investigating potential complications:

- *Additional pulmonary function studies* (e.g., lung volumes and inspiratory and expiratory flow volume loops) may be indicated, especially if there are questions about coexisting chronic obstructive pulmonary disease, a restrictive defect, or possible central airway obstruction. A *diffusing capacity test* is helpful in differentiating between asthma and emphysema in patients at risk for both illnesses, such as smokers and older patients.
- *Assessment of diurnal variation in peak expiratory flow over 1 to 2 weeks* is recommended when patients have asthma symptoms but normal spirometry (Enright et al. 1994). PEF is generally lowest on

FIGURE 1-3. CLASSIFICATION OF ASTHMA SEVERITY

Clinical Features Before Treatment*

	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	<ul style="list-style-type: none"> ■ Continual symptoms ■ Limited physical activity ■ Frequent exacerbations 	Frequent	<ul style="list-style-type: none"> ■ FEV₁ or PEF ≤ 60% predicted ■ PEF variability > 30%
STEP 3 Moderate Persistent	<ul style="list-style-type: none"> ■ Daily symptoms ■ Daily use of inhaled short-acting beta₂-agonist ■ Exacerbations affect activity ■ Exacerbations ≥ 2 times a week; may last days 	> 1 time a week	<ul style="list-style-type: none"> ■ FEV₁ or PEF > 60% – < 80% predicted ■ PEF variability > 30%
STEP 2 Mild Persistent	<ul style="list-style-type: none"> ■ Symptoms > 2 times a week but < 1 time a day ■ Exacerbations may affect activity 	> 2 times a month	<ul style="list-style-type: none"> ■ FEV₁ or PEF ≥ 80% predicted ■ PEF variability 20–30%
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> ■ Symptoms ≤ 2 times a week ■ Asymptomatic and normal PEF between exacerbations ■ Exacerbations brief (from a few hours to a few days); intensity may vary 	≤ 2 times a month	<ul style="list-style-type: none"> ■ FEV₁ or PEF ≥ 80% predicted ■ PEF variability < 20%

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

** Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

BOX 2. IMPORTANCE OF SPIROMETRY IN ASTHMA DIAGNOSIS

Objective assessments of pulmonary function are necessary for the diagnosis of asthma because medical history and physical examination are not reliable means of excluding other diagnoses or of characterizing the status of lung impairment. Although physicians generally seem able to identify a lung abnormality as obstructive (Russell et al. 1986), they have a poor ability to assess the degree of airflow obstruction (Shim and Williams 1980) or to predict whether the obstruction is reversible (Russell et al. 1986).

For diagnostic purposes, spirometry is generally recommended over measurements by a peak flow meter

in the clinician's office because there is wide variability even in the best published peak expiratory flow reference values. Reference values need to be specific to each brand of peak flow meter, and such normative brand-specific values currently are not available for most brands. Peak flow meters are designed as monitoring, not as diagnostic, tools in the office (see component 1-Periodic Assessment and Monitoring). However, peak flow monitoring can establish peak flow variability and thus aid in the determination of asthma severity when patients have asthma symptoms and normal spirometry (see Additional Studies section, page 19).

FIGURE 1-4a. SAMPLE SPIROMETRY VOLUME TIME AND FLOW VOLUME CURVES

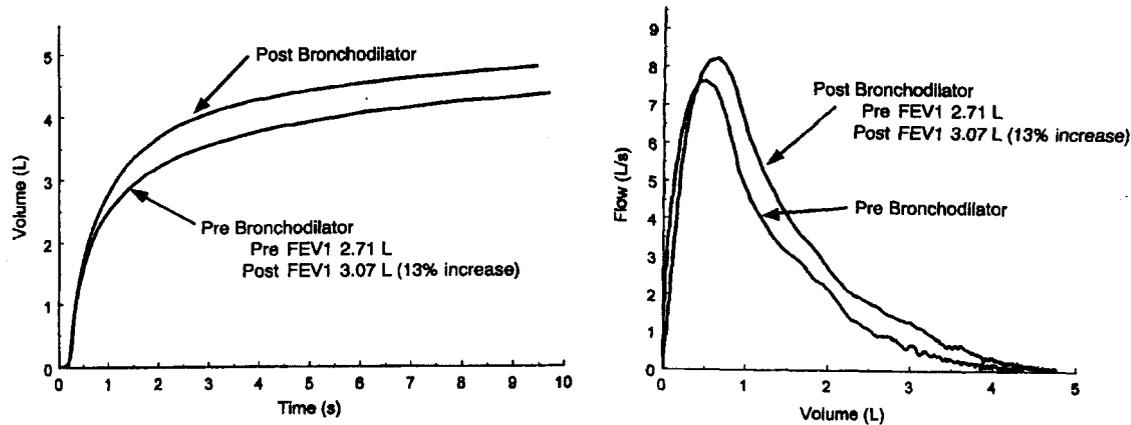


FIGURE 1-4b. REPORT OF SPIROMETRY FINDINGS PRE AND POST BRONCHODILATOR

Pre Bronchodilator				Post Bronchodilator			
Study: bronch	ID:	Test date: 8/7/96	Time: 9:38 am	Study: bronch	ID:	Test date: 8/7/96	Time: 11:42 am
Age: 59	Height: 175 cm	Sex: M	System: 7 20 17	Age: 59	Height: 175 cm	Sex: M	System: 7 20 17
Trial	FVC	FEV1	FEV1/FVC%	Trial	FVC	FEV1	FEV1/FVC%
1	4.34	2.68	61.8%	1	4.68	3.00	64.0%
2	4.40	2.59	58.9%	2	4.73	2.94	62.2%
3	4.44	2.62	58.9%	3	4.59	2.95	64.3%
4	4.56	2.69	58.9%	4	4.76	3.07	64.5%
5	4.55	2.71	59.6%	5	4.78	3.04	63.5%
Best Values	4.56	2.71	59.4%	Best values	4.78	3.07	64.3%
Predicted Values-1	4.23	3.40	80.5%	Reference Values	4.56	2.71	
LLN-2	3.10	2.62	69.9%	Difference (L)	0.22	0.36	
Percent Predicted	107.8%	79.7%	73.8%	Difference (%)	4.8%	13.4%	
Interpretations: Pre-shift FEV ₁ /FVC are below normal range. The reduced rate which air is exhaled indicates obstruction to airflow.				Interpretations: Bronchodilator Response			
1- Predicted values from Knudson et al., <i>Am Rev Respir Dis</i> 1983.				Significant increases in FEV ₁ , with bronchodilator (>12% increase after bronchodilator indicates a significant change).			
2- LLN is the Lower Limit of the Normal range (95th percentile).							

first awakening and highest several hours before the midpoint of the waking day (e.g., between noon and 2 p.m.) (Quackenboss et al. 1991). Optimally, PEF should be measured close to those two times, before taking an inhaled short-acting beta₂-agonist in the morning and after taking one in the afternoon. A 20 percent difference between morning and afternoon measurements suggests asthma. Measuring PEF on waking and in the evening may be more practical and feasible, but values will tend to underestimate the actual diurnal variation.

- *Bronchoprovocation* with methacholine, histamine, or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal.

For safety reasons, bronchoprovocation testing should be carried out by a trained individual in an appropriate facility and is not generally recommended if the FEV₁ is <65 percent predicted. A negative bronchoprovocation may be helpful to rule out asthma.

- *Chest x ray* may be needed to exclude other diagnoses.
- *Allergy testing* (see component 2).
- *Evaluation of the nose for nasal polyps and sinuses for sinus disease.*
- *Evaluation for gastroesophageal reflux* (Harding and Richter 1992) (see component 2).

FIGURE 1-5. DIFFERENTIAL DIAGNOSTIC POSSIBILITIES FOR ASTHMA

Infants and Children

Upper airway diseases

- Allergic rhinitis and sinusitis

Obstructions involving large airways

- Foreign body in trachea or bronchus
- Vocal cord dysfunction
- Vascular rings or laryngeal webs
- Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
- Enlarged lymph nodes or tumor

Obstructions involving small airways

- Viral bronchiolitis or obliterative bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Heart disease

Other causes

- Recurrent cough not due to asthma
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux

Adults

- Chronic obstructive pulmonary disease (chronic bronchitis or emphysema)
- Congestive heart failure
- Pulmonary embolism
- Laryngeal dysfunction
- Mechanical obstruction of the airways (benign and malignant tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (angiotensin-converting enzyme [ACE] inhibitors)
- Vocal cord dysfunction

The usefulness of measurements of biomarkers of inflammation (e.g., total and differential cell count and mediator assays) in sputum, blood, or urine as aids to the diagnosis of asthma is currently being evaluated in clinical research trials.

DIFFERENTIAL DIAGNOSIS OF ASTHMA

Recurrent episodes of cough and wheezing are almost always due to asthma in both children and adults. Underdiagnosis of asthma is a frequent problem, especially in children who wheeze when they have respiratory infections. These children are often labeled as having bronchitis, bronchiolitis, or pneumonia even though the signs and symptoms are most compatible with a diagnosis of asthma. However, the clinician needs to be aware of other causes of airway obstruction leading to wheezing (see figure 1-5).

There are two general patterns of wheezing in infancy: nonallergic and allergic. Nonallergic infants wheeze when they have an acute upper respiratory viral infection, but as their airways grow larger in the preschool years the wheezing disappears. Allergic infants also wheeze with viral infections, but they are more likely to have asthma that will continue throughout childhood. This group may have eczema, allergic rhinitis, or food allergy as other manifestations of allergy. Both groups may benefit from asthma treatment (see Infants and Young Children section, page 94, in component 3-Managing Asthma Long Term).

Vocal cord dysfunction often mimics asthma. Patients with vocal cord dysfunction can present with recurrent severe shortness of breath and wheezing. Vocal cord dysfunction may even cause alveolar hypoventilation, with increases in PCO_2 that prompt urgent intubation and mechanical ventilation. Vocal cord dysfunction that mimics asthma is more common in young adults with psychological disorders. It should be suspected when physical examination reveals a monophonic wheeze heard loudest over the glottis. Further evaluation by flow-volume curve revealing inspiratory flow limitation strongly supports the diagnosis of vocal cord dysfunction. Definitive diagnosis—and exclusion of organic causes of vocal cord narrowing—requires direct visualization of the vocal cords. Treatment with speech therapy that teaches techniques for relaxed throat breathing is often effective (Newman et al. 1995; Bucca et al. 1995; Christopher et al. 1983).

GENERAL GUIDELINES FOR REFERRAL TO AN ASTHMA SPECIALIST

Criteria for the referral of an asthma patient have been developed (Spector and Nicklas 1995; Shuttari 1995). Based on the opinion of the Expert Panel, referral for consultation or care to a specialist in asthma care (usually, a fellowship-trained allergist or pulmonologist; occasionally, other physicians with expertise in asthma management developed through additional training and experience) is recommended when:

- Patient has had a life-threatening asthma exacerbation.
- Patient is not meeting the goals of asthma therapy (see component 1-Periodic Assessment and Monitoring) after 3 to 6 months of treatment. An earlier referral or consultation is appropriate if the physician concludes that the patient is unresponsive to therapy.
- Signs and symptoms are atypical or there are problems in differential diagnosis.
- Other conditions complicate asthma or its diagnosis (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis, vocal cord dysfunction, gastroesophageal reflux, chronic obstructive pulmonary disease).
- Additional diagnostic testing is indicated (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy).
- Patient requires additional education and guidance on complications of therapy, problems with adherence, or allergen avoidance.
- Patient is being considered for immunotherapy.
- Patient has severe persistent asthma, requiring step 4 care (referral may be considered for patients requiring step 3 care; see component 3-Managing Asthma Long Term).
- Patient requires continuous oral corticosteroid therapy or high-dose inhaled corticosteroids or has required more than two bursts of oral corticosteroids in 1 year.
- Patient is under age 3 and requires step 3 or 4 care (see component 3-Managing Asthma Long Term). When patient is under age 3 and requires step 2 care or initiation of daily long-term therapy, referral should be considered.
- Patient requires confirmation of a history that suggests that an occupational or environmental inhalant or ingested substance is provoking or contributing to asthma. Depending on the complexities of diagnosis, treatment, or the intervention required in the work environment, it may be appropriate in some cases for the specialist to manage the patient over a period of time or comanage with the primary care provider.

In addition, patients with significant psychiatric, psychosocial, or family problems that interfere with their asthma therapy may need referral to an appropriate mental health professional for counseling or treatment. These characteristics have been shown to interfere with a patient's ability to adhere to treatment (Strunk 1987; Strunk et al. 1985)

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Component 1: Measures of Assessment and Monitoring

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Periodic Assessment and Monitoring: Essential for Asthma Management

KEY POINTS

- The goals of therapy are to:
 - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
 - Maintain (near) "normal" pulmonary function
 - Maintain normal activity levels (including exercise and other physical activity)
 - Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
 - Provide optimal pharmacotherapy with least amount of adverse effects
 - Meet patients' and families' expectations of and satisfaction with asthma care
- Periodic assessments and ongoing monitoring of asthma are recommended to determine if the goals of therapy are being met. Measurements of the following are recommended:
 - Signs and symptoms of asthma
 - Pulmonary function
 - Quality of life/functional status
 - History of asthma exacerbations
 - Pharmacotherapy
 - Patient-provider communication and patient satisfaction
- Clinician assessment and patient self-assessment are the primary methods for monitoring asthma. Population-based assessment is beginning to be used by managed care organizations.
- Spirometry tests are recommended (1) at the time of initial assessment, (2) after treatment is initiated and symptoms and PEF have stabilized, and (3) at least every 1 to 2 years.
- Patients should be given a written action plan based on signs and symptoms and/or PEF; this is especially important for patients with moderate-to-severe persistent asthma or a history of severe exacerbations.
- Patients should be trained to recognize symptom patterns indicating inadequate asthma control and the need for additional therapy.
- Recommendations on how and when to do peak flow monitoring are presented.

DIFFERENCES FROM 1991 EXPERT PANEL REPORT

- The new report includes an additional goal of therapy (meet patients' and families' expectations of and satisfaction with asthma care) that was not listed in the 1991 report.
- Periodic assessment of six domains of patient health that correspond with the goals of asthma therapy are now recommended, including signs and symptoms, pulmonary function, quality of life, history of exacerbations, pharmacotherapy, and patient-provider communication and patient satisfaction.
- The following changes affecting peak flow monitoring have been made:
 - The recommendation for peak flow monitoring was changed from twice daily to morning. If the morning reading is less than 80 percent of personal best PEF, more frequent peak flow monitoring may be desired.

- Discussion of inconsistencies in measurement among peak flow meters was added.
 - Use of the individual patient's personal best PEF is emphasized strongly.
- The recommendation for patients at all severity levels to monitor symptoms to recognize early signs of deterioration is emphasized.
 - Sample questions to use in periodic assessments were added.

GOALS OF THERAPY

The purpose of periodic assessment and ongoing monitoring is to determine whether the goals of asthma therapy are being achieved. The goals of therapy are as follows:

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

ASSESSMENT MEASURES

The Expert Panel recommends ongoing monitoring in the six areas listed below to determine whether the goals of therapy are being met. The assessment measures for monitoring these six areas are described in this section and are recommended based on the opinion of the Expert Panel.

- Monitoring signs and symptoms of asthma
- Monitoring pulmonary function
 - Spirometry
 - Peak flow monitoring
- Monitoring quality of life/functional status
- Monitoring history of asthma exacerbations
- Monitoring pharmacotherapy
- Monitoring patient-provider communication and patient satisfaction

Monitoring Signs and Symptoms of Asthma

Every patient with asthma should be taught to recognize symptom patterns that indicate inadequate asthma control (see Patient Self-Assessment section, page 38, and component 4). Symptom monitoring should be used as a means to determine the need for intervention, including additional medication, in the context of an action plan (see figure 4-5).

Symptoms and clinical signs of asthma should be assessed at each health care visit through physical examination and appropriate questions. This is crucial to optimal asthma care. A description of the important elements of an asthma-related physical examination can be found in component 1-Initial Assessment and Diagnosis, which also discusses the variability in the types of symptoms associated with asthma.

Detailed patient recall of symptoms decreases over time; therefore, the Expert Panel recommends that any detailed symptoms history be based on a short (2 to 4 weeks) recall period. For example, the clinician may choose to assess over a 2-week, 3-week, or 4-week recall period. Symptom assessment for periods longer than 4 weeks should reflect more global symptom assessment, such as inquiring whether the patient's asthma has been better or worse since the last visit and inquiring whether the patient has encountered any particular difficulties during specific seasons or events. Figure 1-6 provides an example of a set of questions that can be used to characterize both global (long-term recall) and recent (short-term recall) asthma symptoms.

In addition, any assessment of the patient's symptom history should include at least three key symptom expressions:

- Daytime asthma symptoms (including wheezing, cough, chest tightness, or shortness of breath)

**FIGURE 1-6. COMPONENTS OF THE CLINICIAN'S FOLLOWUP ASSESSMENT:
SAMPLE ROUTINE CLINICAL ASSESSMENT QUESTIONS***

Monitoring Signs and Symptoms

(Global assessment) "Has your asthma been better or worse since your last visit?"

(Recent assessment) "In the past 2 weeks, how many days have you:

- Had problems with coughing, wheezing, shortness of breath, or chest tightness during the day?"
- Awakened at night from sleep because of coughing or other asthma symptoms?"
- Awakened in the morning with asthma symptoms that did not improve within 15 minutes of inhaling a short-acting inhaled beta₂-agonist?"
- Had symptoms while exercising or playing?"

Monitoring Pulmonary Function

Lung Function

"What is the highest and lowest your peak flow has been since your last visit?"

"Has your peak flow dropped below ____ L/min (80 percent of personal best) since your last visit?"

"What did you do when this occurred?"

Peak Flow Monitoring Technique

"Please show me how you measure your peak flow."

"When do you usually measure your peak flow?"

Monitoring Quality of Life/Functional Status

"Since your last visit, how many days has your asthma caused you to:

- Miss work or school?"
- Reduce your activities?"
- (For caregivers) Change your activity because of your child's asthma?"

"Since your last visit, have you had any unscheduled or emergency department visits or hospital stays?"

Monitoring Exacerbation History

"Since your last visit, have you had any episodes/times when your asthma symptoms were a lot worse than usual?"

If yes - "What do you think caused the symptoms to get worse?"

If yes - "What did you do to control the symptoms?"

"Have there been any changes in your home or work environment (e.g., new smokers or pets)?"

Monitoring Pharmacotherapy

Medications

"What medications are you taking?"

"How often do you take each medication?"

"How much do you take each time?"

"Have you missed or stopped taking any regular doses of your medications for any reason?"

"Have you had trouble filling your prescriptions (e.g., for financial reasons, not on formulary)?"

"How many puffs of your short-acting inhaled beta₂-agonist (quick-relief medicine) do you use per day?"

"How many [name short-acting inhaled beta₂-agonist] inhalers [or pumps] have you been through in the past month?"

"Have you tried any other medicines or remedies?"

Side Effects

"Has your asthma medicine caused you any problems?"

- Shakiness, nervousness, bad taste, sore throat, cough, upset stomach

Inhaler Technique

"Please show me how you use your inhaler."

Monitoring Patient-Provider Communication and Patient Satisfaction

"What questions have you had about your asthma daily self-management plan and action plan?"

"What problems have you had following your daily self-management plan? Your action plan?"

"Has anything prevented you from getting the treatment you need for your asthma from me or anyone else?"

"Have the costs of your asthma treatment interfered with your ability to get asthma care?"

"How satisfied are you with your asthma care?"

"How can we improve your asthma care?"

"Let's review some important information:"

- "When should you increase your medications? Which medication(s)?"
- "When should you call me [your doctor or nurse practitioner]? Do you know the after-hours phone number?"
- "If you can't reach me, what emergency department would you go to?"

* These questions are examples and do not represent a standardized assessment instrument. The validity and reliability of these questions have not been assessed.

- Nocturnal awakening as a result of asthma symptoms
- Asthma symptoms early in the morning that are not improved 15 minutes after inhaling a short-acting beta₂-agonist

Monitoring Pulmonary Function

In addition to assessing symptoms, it is also important to periodically assess pulmonary function. The main methods are spirometry and peak flow monitoring.

Regular monitoring of pulmonary function is particularly important for asthma patients who do not perceive their symptoms until airflow obstruction is severe. Currently, there is no readily available method of detecting the "poor perceivers." The literature reports that patients who had a near-fatal asthma exacerbation, as well as older patients, are more likely to have poor perception of airflow obstruction (Kikuchi et al. 1994; Connolly et al. 1992).

Spirometry

The Expert Panel recommends that spirometry tests be done (1) at the time of initial assessment; (2) after treatment is initiated and symptoms and peak expiratory flow (PEF) have stabilized, to document attainment of (near) "normal" airway function; and (3) at least every 1 to 2 years to assess the maintenance of airway function.

Spirometry may be indicated more often than every 1 to 2 years, depending on the clinical severity and response to management. Spirometry with measurement of the FEV₁ is also useful:

- As a periodic (e.g., yearly) check on the accuracy of the peak flow meter (Miles et al. 1995)
- When more precision is desired in measuring lung function (e.g., when evaluating response to bronchodilator or nonspecific airway responsiveness or when assessing response to a "step down" in pharmacotherapy)
- When PEF results are unreliable (e.g., in some very young or elderly patients or when neuromuscular or orthopedic problems are present) and the physician needs the quality checks that are available only with spirometry (Hankinson and Wagner 1993).

For routine monitoring at most outpatient visits, measurement of PEF with a peak flow meter is generally a sufficient assessment of pulmonary function, particularly in mild intermittent, mild persistent, and moderate persistent asthma.

Peak Flow Monitoring

Peak expiratory flow provides a simple, quantitative, and reproducible measure of the existence and severity of airflow obstruction. PEF can be measured with inexpensive and portable peak flow meters. *It must be stressed that peak flow meters are designed as tools for ongoing monitoring, not diagnosis.* Because the measurement of PEF is dependent on effort and technique, patients need instructions, demonstrations, and frequent reviews of technique (see figure 1-7, the patient handout *How To Use Your Peak Flow Meter*).

Peak flow monitoring can be used for short-term monitoring, managing exacerbations, and daily long-term monitoring. When used in these ways, the patient's measured personal best is the most appropriate reference value. Four studies (Woolcock et al. 1988; Ignacio-Garcia and Gonzalez-Santos 1995; Lahdensuo et al. 1996; Beasley et al. 1989) have found that comprehensive asthma self-management programs, in which peak flow monitoring was a component, achieved significant improvements in health outcomes. Thus far, the few studies that have isolated a comparison of peak flow and symptom monitoring have not been sufficient to assess the relative contributions of each to asthma management (see box 1, *Peak Flow Monitoring Literature Review*). The literature does suggest which patients may benefit most from peak flow monitoring. The Expert Panel concludes, on the basis of this literature and the Panel's opinion, that:

- Patients with moderate-to-severe persistent asthma should learn how to monitor their PEF and have a peak flow meter at home.
- Peak flow monitoring during exacerbations of asthma is recommended for patients with moderate-to-severe persistent asthma to:
 - Determine severity of the exacerbation
 - Guide therapeutic decisions (see component 3-Managing Exacerbations and figure 4-5) in the home, clinician's office, or emergency department

How To Use Your Peak Flow Meter

A peak flow meter is a device that measures how well air moves out of your lungs. During an asthma episode, the airways of the lungs usually begin to narrow slowly. The peak flow meter may tell you if there is narrowing in the airways hours—sometimes even days—before you have any asthma symptoms.

By taking your medicine(s) early (before symptoms), you may be able to stop the episode quickly and avoid a severe asthma episode. Peak flow meters are used to check your asthma the way that blood pressure cuffs are used to check high blood pressure.

The peak flow meter also can be used to help you and your doctor:

- Learn what makes your asthma worse
- Decide if your treatment plan is working well
- Decide when to add or stop medicine
- Decide when to seek emergency care

A peak flow meter is most helpful for patients who must take asthma medicine daily. Patients age 5 and older are usually able to use a peak flow meter. Ask your doctor or nurse to show you how to use a peak flow meter.

How To Use Your Peak Flow Meter

- Do the following five steps with your peak flow meter:
 1. Move the indicator to the bottom of the numbered scale.
 2. Stand up.
 3. Take a deep breath, filling your lungs completely.

4. Place the mouthpiece in your mouth and close your lips around it. Do not put your tongue inside the hole.

5. Blow out as hard and fast as you can in a single blow.

- Write down the number you get. But if you cough or make a mistake, don't write down the number. Do it over again.
- Repeat steps 1 through 5 two more times and write down the best of the three blows in your asthma diary.

Find Your Personal Best Peak Flow Number

Your personal best peak flow number is the highest peak flow number you can achieve over a 2- to 3-week period when your asthma is under good control. Good control is when you feel good and do not have any asthma symptoms.

Each patient's asthma is different, and your best peak flow may be higher or lower than the peak flow of someone of your same height, weight, and sex. This means that it is important for you to find your own personal best peak flow number. Your treatment plan needs to be based on your own personal best peak flow number.

To find out your personal best peak flow number, take peak flow readings:

- At least twice a day for 2 to 3 weeks.
- When you wake up and between noon and 2:00 p.m.
- Before and after you take your short-acting inhaled beta₂-agonist for quick relief, if you take this medicine.
- As instructed by your doctor.

How To Use Your Peak Flow Meter (CONTINUED)

The Peak Flow Zone System

Once you know your personal best peak flow number, your doctor will give you the numbers that tell you what to do. The peak flow numbers are put into zones that are set up like a traffic light. This will help you know what to do when your peak flow number changes. For example:

Green Zone (more than ___ L/min [80 percent of your personal best number]) signals *good control*. No asthma symptoms are present. Take your medicines as usual.

Yellow Zone (between ___ L/min and ___ L/min [50 to less than 80 percent of your personal best number]) signals *caution*. You must take a short-acting inhaled beta₂-agonist right away. Also, your asthma may not be under good day-to-day control. Ask your doctor if you need to change or increase your daily medicines.

Red Zone (below ___ L/min [50 percent of your personal best number]) signals a *medical alert*. You must take a short-acting inhaled beta₂-agonist (quick-relief medicine) right away. Call your doctor or emergency room and ask what to do, or go directly to the hospital emergency room.

Record your personal best peak flow number and peak flow zones in your asthma diary.

Use the Diary To Keep Track of Your Peak Flow

Measure your peak flow when you wake up, *before* taking medicine. Write down your peak flow number in the diary every day, or as instructed by your doctor.

Actions To Take When Peak Flow Numbers Change

- PEF goes between ___ L/min and ___ L/min (50 to less than 80 percent of personal best, yellow zone).
ACTION: Take a short-acting inhaled beta₂-agonist (quick-relief medicine) as prescribed by your doctor.
- PEF increases 20 percent or more when measured before and after taking a short-acting inhaled beta₂-agonist (quick-relief medicine).
ACTION: Talk to your doctor about adding more medicine to control your asthma better (for example, an anti-inflammatory medication).

BOX 1. PEAK FLOW MONITORING LITERATURE REVIEW

Seven intervention studies on the use of daily peak flow monitoring for asthma management were identified, six through a MEDLINE search from 1980 to 1995 and reviews of reference lists and one from the 1996 literature.

Three randomized controlled trials (Woolcock et al. 1988, N=24; Ignacio-Garcia and Gonzalez-Santos 1995, N=70; Lahdensuo et al. 1996, N=115) and an uncontrolled pretest/posttest study (Beasley et al. 1989, N=36) tested comprehensive asthma interventions that included self-management medication plans, medications, education, and peak flow monitoring. These studies reported significant improvements in lung function, symptoms, and medication use after 6 months (Beasley et al. 1989; Ignacio-Garcia and Gonzalez-Santos 1995) and 18 months (Woolcock et al. 1988). However, these studies could not determine the relative importance of peak flow monitoring to the effectiveness of the comprehensive asthma intervention.

Three randomized controlled trials compared the use of daily peak flow monitoring with symptom monitoring (Charlton et al. 1990, N=115 adults and children) or usual care (Grampian Asthma Study 1994, N=569 adults; Jones et al. 1995, N=72 adults). These studies found no significant differences between the experimental and control groups in the outcomes measured: lung function, symptom frequency, quality of life, hospitalizations, medication use, and medical consultations. However, one of these studies involved patients with mild asthma (Jones et al. 1995), a population not expected to benefit as much from peak flow monitoring.

Almost all the peak flow monitoring studies available had study design and execution problems (e.g., selection bias, unequal control and experimental groups, small sample sizes, high loss to followup). More studies of daily long-term peak flow monitoring among patients with moderate and severe persistent asthma are urgently needed. Nonetheless, some issues suggested by the few studies available warrant consideration:

- Among patients with mild intermittent or mild persistent asthma, there appears to be no significant advantage of peak flow monitoring over usual care without peak flow monitoring (Jones et al. 1995).
- Patients with moderate-to-severe persistent asthma or unstable asthma are more likely to benefit from long-term daily peak flow monitoring. For example, the Grampian study authors conducted an observational study of 89 patients disqualified from the original study because their asthma was too severe and found that those who used peak flow meters took oral corticosteroids more often (action plan told patients to take oral corticosteroids at specific PEF levels) and had significantly fewer days of limited activity than those who did not use a peak flow meter.
- Short-term daily peak flow monitoring is helpful for assessing the severity of a patient's asthma and evaluating response to chronic maintenance therapy.
- Short-term peak flow monitoring is also helpful during exacerbations for assessing the severity of acute airflow obstruction and evaluating the patient's response to bronchodilator therapy. Janson-Bjerklie and Shnell (1988) found that patients used medications less frequently when they monitored PEF during symptomatic periods.
- Additional studies are needed to clarify the role of long-term daily peak flow monitoring in detecting early signs of deterioration, especially for patients with moderate-to-severe persistent asthma. Studies have found that 15 percent of asthma patients (Rubinfeld and Pain 1976), 24 to 27 percent of elderly patients (Connolly et al. 1992), and patients who had near-fatal asthma exacerbations (Kikuchi et al. 1994) could not perceive significant reductions in FEV₁ provoked by methacholine challenge. A recent study in a general community setting found that for 60 percent of patients, their PEF did not correlate with the perception of how well their asthma was controlled (i.e., patients felt their asthma was better than the PEF readings indicated) (Kendrick et al. 1993). However, symptom monitoring and peak flow monitoring were found to be equally effective in identifying exacerbations that were confirmed by FEV₁ measurements in a randomized controlled, crossover study (Malo et al. 1993). Although peak flow monitoring for children may be

BOX 1. PEAK FLOW MONITORING LITERATURE REVIEW (CONTINUED)

helpful, one study points out that the variability of individual PEF measurements between different brands of peak flow meters and in comparison to spirometry warrants caution about teaching how to use peak flow meters and interpret the measurements. Emphasis should be placed on observing *differences* between readings over time rather than on a single reading (Sly et al. 1994).

- Patient preferences regarding peak flow monitoring vary. One study found that most patients felt that peak flow monitoring was helpful (Jones et al. 1995), another found that most patients felt symptom monitoring was helpful (Garrett et al. 1994), and another study found that most patients felt that both forms of monitoring combined were helpful (D'Souza et al. 1994). In an observational study of children attending a community clinic, 70 percent of the parents of

children using peak flow monitoring reported it to be very useful, especially for judging the severity of an exacerbation and the child's response to inhaled short-acting beta₂-agonist (Lloyd and Ali 1992).

- Linking peak flow monitoring to specific asthma management plans and providing appropriate instruction and feedback to the patient will influence the effectiveness and perceived usefulness of peak flow monitoring.

Due to the limited number and quality of the studies on peak flow monitoring reported thus far, the Expert Panel believes that more research is urgently needed in this area. Recent studies do offer some guidance on which patients are most likely to benefit from daily peak flow monitoring; see text of the report for recommendations.

- Long-term daily peak flow monitoring is helpful in managing patients with moderate-to-severe persistent asthma to:

- Detect early changes in disease status that require treatment
- Evaluate responses to changes in therapy
- Provide assessment of severity for patients with poor perception of airflow obstruction
- Afford a quantitative measure of impairment

- If long-term daily peak flow monitoring is not used, a short-term (2 to 3 weeks) period of peak flow monitoring is recommended to:

- Evaluate responses to changes in chronic maintenance therapy
- Identify temporal relationship between changes in PEF and exposure to environmental or occupational irritants

or allergens. It may be necessary to record PEF four or more times a day (Chan-Yeung 1995).

- Establish the individual patient's personal best PEF

- The Expert Panel does not recommend long-term daily peak flow monitoring for patients with mild intermittent or mild persistent asthma unless the patient/family and/or clinician find it useful in guiding therapeutic decisions. Any patient who develops severe exacerbations may benefit from peak flow monitoring.

Limitations of long-term peak flow monitoring include:

- Difficulty in maintaining adherence to monitoring (Reeder et al. 1990; Chmelik and Doughty 1994; Malo et al. 1993), often due to inconvenience, lack of required level of motivation, or lack of a specific treatment plan based on PEF
- Potential for incorrect readings related to poor technique, misinterpretation, or device failure

Whether peak flow monitoring, symptom monitoring, or a combination of approaches is used, the Expert Panel believes that self-monitoring is important to the effective self-management of asthma. The nature and intensity of self-monitoring should be individualized, based on such factors as asthma severity, patient's ability to perceive airflow obstruction, availability of peak flow meters, and patient preferences.

It is the opinion of the Expert Panel that, regardless of the type of monitoring used, patients should be given a written action plan and be instructed to use it (see figure 4-5). The Panel believes it is especially important to give a written action plan to patients with moderate-to-severe persistent asthma and any patient with a history of severe exacerbations. The action plan will describe the actions patients should take based on their signs and symptoms and/or PEF. The clinician should periodically review the plan, revise it as necessary, and confirm that the patient knows what to do if his or her asthma gets worse.

Recommendations on How To Monitor Peak Flow. The Expert Panel recommends that patients who are using a peak flow meter be instructed on how to establish their personal best peak expiratory flow (figure 1-7) and use it as the basis of their action plan (figure 4-5). Meters used to measure PEF should meet American Thoracic Society recommendations for monitoring devices (American Thoracic Society 1995).

The patient's personal best PEF can be estimated after a 2- to 3-week period in which the patient records PEF two to four times per day. The personal best value is usually achieved in the early afternoon measurement after maximal therapy has stabilized the patient (Quackenboss et al. 1991). A course of oral corticosteroids may be needed to establish the personal best PEF. The patient's personal best value should be reassessed periodically to account for progression of disease in children and adults and for growth in children. Occasionally, a PEF value is recorded that is markedly higher than other values. This may be due to "spitting" (especially if the peak flow meter mouthpiece is small) or coughing into the peak flow meter, as well as other reasons that are not well understood. Therefore, caution should be used in establishing a personal best value when an outlying value is observed. Children with moderate-to-severe persistent asthma should repeat the short-term

monitoring period every 6 months to establish changes in personal best PEF that occur with growth.

Patients requiring daily peak flow monitoring should measure their PEF on waking from sleep in the morning before taking a bronchodilator, if the patient uses a bronchodilator (Reddel et al. 1995; Morris et al. 1994). When the morning PEF is below 80 percent of the patient's personal best, PEF should be measured more than once a day (again, before taking a bronchodilator). This recommendation is based not on scientific data, but on the logic of reducing delays in treatment. The additional measurements of PEF during the day will enable patients to detect if their asthma is continuing to worsen or is improving after taking medication. If their asthma is worsening, they will have the opportunity to quickly respond to this. In addition, periodically having patients take their PEF first thing in the morning and in the early afternoon for 1 to 2 weeks will assess airflow variability, which is an indicator of the current level of the patient's asthma severity (see figure 1-3 and Additional Studies section, page 19).

It is the Expert Panel's opinion that, in general, PEF below 80 percent of the patient's personal best before bronchodilator inhalation indicates a need for additional medication. PEF below 50 percent indicates a severe asthma exacerbation (see component 3 for recommended treatment). These cutpoints of 80 and 50 percent of the personal best are somewhat arbitrary. The emphasis is not on a specific PEF value but, rather, on a patient's change from personal best or from one reading to the next. Cutpoints should be tailored to individual patients' needs and PEF patterns.

Cutpoints may be easier to use and remember when they are adapted to a traffic light system (see figure 4-5) (Lewis et al. 1984; Mendoza et al. 1988; Plaut 1995). In this system, for example, the green zone (80 to 100 percent of personal best) signals good control, the yellow zone (50 to less than 80 percent of personal best) signals caution, and the red zone (below 50 percent of personal best) signals a medical alert (see figure 1-7). Because the yellow zone includes a wide spectrum of asthma severity, clinicians may consider recommending different interventions for a high yellow zone (e.g., 65 to less than 80 percent of personal best) and a low yellow zone (e.g., 50 to less than 65 percent of personal best).

BOX 2. DIFFERENCES IN PEAK FLOW ACROSS RACIAL AND ETHNIC POPULATIONS

Currently available normative standards for PEF use standing height as well as age and sex as predictors. However, for a given height, African Americans have longer legs, shorter trunks, and smaller thoracic diameters (Woolcock et al. 1972; Coultas et al. 1994). The normal ranges of lung function in Hispanics, Asians, and Native Americans have received less attention (Coultas et al. 1994). Differences have been reported among Caucasians and Japanese Americans (Marcus et al. 1988; Coultas et al. 1994), Native Americans (Wall et al. 1982; Crapo et al. 1988; Marcus et al. 1988), and Latinos (Hsu et al. 1979; Coultas et al. 1988, 1994). But these results are inconsistent, especially for Hispanics and Native Americans (Coultas et al. 1994). In general, lung function for these groups tends to be intermediate between those of Caucasians and African Americans.

Because predicted normal lung function varies across racial and ethnic populations, it is the opinion of the Expert Panel that (1) normative standards for PEF derived from a given racial or ethnic group cannot be readily extrapolated to other groups and that (2) the most clinically useful standard for ongoing monitoring of asthma is the patient's personal best PEF value.

The Expert Panel recommends that patients use the same peak flow meter over time and bring their peak flow meter for use at every followup visit. Using the same brand of meter is recommended because different brands of meters can give significantly different values (Jackson 1995; Enright et al. 1995; Hegewald et al. 1995; Siy et al. 1994; Miller et al. 1992) and because lung function varies across racial and ethnic populations. (See box 2, Differences in Peak Flow Across Racial and Ethnic Populations.) Thus, there is no universal normative standard for PEF. In addition, brand-specific normative values are not available for most peak flow meters.

Despite this variability across different brands of peak flow meters, measurements from the same meter and meters of the same brand are fairly consistent in measuring PEF (Jackson 1995; Enright et al. 1995; Hegewald et al. 1995; Siy et al. 1994; Miller et al. 1992). Thus, once patients establish their personal best PEF on their own meter, they can obtain reliable

and clinically meaningful readings of their PEF. However, at each visit, the patient's peak flow meter should be inspected. At least once a year, or any time there is a question about the validity of peak flow meter readings, PEF values from the portable peak flow meter and from laboratory spirometry should be compared.

When patients replace their peak flow meter, it is prudent to have them reestablish their personal best PEF with the new meter, regardless of whether the replacement meter is the same brand as the original. Action plan cutpoints also may need to be modified. The durability and consistency over time of peak flow meters have not been adequately studied to provide guidance on when a peak flow meter needs to be replaced.

Monitoring Quality of Life/Functional Status

To determine whether the goals of asthma therapy are being met, it is crucial to examine how the disease expression and control are affecting the patient's quality of life. Several dimensions of quality of life may be important to track, including physical function, role function, and mental health function. Several comprehensive survey instruments, such as the SF-36 (Stewart et al. 1988 for adult measure; Landgraf et al. 1996 for child measure), have been developed for general use for patient populations. In addition, a number of asthma-specific quality-of-life survey instruments have been developed (Creer et al. 1989; Hyland et al. 1991; Juniper et al. 1992; Marks et al. 1993; Richards and Hemstreet 1994), several of which appear promising. However, certain concerns preclude the Expert Panel from recommending the general adoption of these instruments at this time, such as the lack of experience with the use of the instruments in clinical practice and the time involved in administering the surveys. The Expert Panel does recommend that at least several key areas of quality of life be periodically assessed for each person with asthma. These include:

- Any missed work or school due to asthma
- Any reduction in usual activities (either home/work/school or recreation/exercise)
- Any disturbances in sleep due to asthma
- Any change in caregiver activities due to a child's asthma (for caregivers of children with asthma)

Figure 1-6 provides a set of questions that the Expert Panel recommends for use in characterizing quality-of-life concerns for persons with asthma (also see figure 4-2).

Monitoring History of Asthma Exacerbations

Exacerbations of asthma are characterized by periods of increased symptoms and reduced lung function, which may result in diminished ability to perform usual activities. Exacerbations may be brought on by exposures to irritants or sensitizers in the home, work, or general environment. Infections, certain medications, and a number of other medical conditions, as well as insufficient or ineffective therapy, also may trigger exacerbations (see component 2).

During periodic assessments, clinicians should question the patient and evaluate any records of patient self-monitoring (figures 1-8 and 1-9) to detect exacerbations, both self-treated and those treated by other health care providers. It is important to evaluate the frequency, severity, and causes of exacerbations. The patient should be asked about precipitating exposures and other factors. Specific inquiry into unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities may be helpful. Severity can be estimated by the increased need for oral corticosteroids. Control of asthma can be assessed by the increased need for short-acting beta₂-agonist. Finally, any hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation. The clinician then can request summaries of all care received to facilitate continuity of care.

Monitoring Pharmacotherapy

To ensure the effectiveness of pharmacotherapy, it is essential that the drug regimen be based on a sound rationale and that it be monitored on an ongoing basis. Based on the opinion of the Expert Panel, the following factors should be monitored: patient adherence to the regimen, inhaler technique, level of usage of as-needed inhaled short-acting beta₂-agonist, frequency of oral corticosteroid "burst" therapy, changes in dosage of inhaled anti-inflammatory or other long-term-control medications, and side effects of medications (see assessment questions in figure 1-6). It is also critical that the clinician determine that the patient is on the appropriate step of pharmacotherapy (see component 3-Managing Asthma Long Term) and

has an up-to-date, written daily self-management plan and action plan (see figures 4-4 and 4-5).

Monitoring Patient-Provider Communication and Patient Satisfaction

Health care providers should routinely assess the effectiveness of patient/provider communication (see figure 1-6). Open and unrestricted communication among the clinician, the patient, and the family is essential to ensure successful self-management by the patient with asthma. Every effort should be made to encourage open discussion of concerns and expectation of therapy. See component 4 for specific strategies to enhance communication and patient adherence to the treatment plan.

Patient satisfaction with their asthma care and resolution of fears and concerns are important goals and will increase adherence to the treatment plan (Haynes et al. 1979; Meichenbaum and Turk 1987). Two aspects of patient satisfaction should be monitored: satisfaction with asthma control and satisfaction with the quality of care. See figures 1-6, 1-8, and 4-2 for examples of questions to use in monitoring patient satisfaction.

ASSESSMENT METHODS

Each of the key measures used in the periodic assessment of asthma (i.e., signs and symptoms, pulmonary function, quality of life, history of exacerbations, pharmacotherapy, and patient-provider communication and patient satisfaction) can be obtained by several methods. The principal methods include clinician assessment and patient (and/or parent or caregiver) self-assessment. In addition, population-based assessment of asthma care is being developed in the managed care field.

Clinician Assessment

Clinical assessment of asthma should be obtained via medical history and physical examination with appropriate pulmonary function testing. Optimal history assessment may be best achieved via a consistent set of questions (figure 1-6); physical examination for asthma is reviewed in component 1-Initial Assessment and Diagnosis. Patients with mild intermittent or mild persistent asthma that has been under control for at least 3 months should be seen by a clinician about every 6 months. This is a rough guideline based on the opinion of the Expert Panel.

FIGURE 1-8. SAMPLE* PATIENT SELF-ASSESSMENT SHEET FOR FOLLOWUP VISITS

Name: _____ Date: _____

How many days in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)? _____0 _____1 _____2 _____3 _____4 _____5 _____6 _____7

How many nights in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)? _____0 _____1 _____2 _____3 _____4 _____5 _____6 _____7

Do you perform peak flow readings at home? _____yes _____no

If yes, did you bring your peak flow chart? _____yes _____no

How many days in the past week has asthma restricted your physical activity? _____0 _____1 _____2 _____3 _____4 _____5 _____6 _____7

Have you had any asthma attacks since your last visit? _____yes _____no

Have you had any unscheduled visits to a doctor, including to the emergency department, since your last visit? _____yes _____no

How many puffs of your short-acting inhaled beta₂-agonist (quick-relief medicine) do you use per day? _____
Average number of puffs per day

How many of your short-acting inhaled beta₂-agonist inhalers did you go through over the past month? _____
Number of inhalers in past month

What questions or concerns would you like to discuss with the doctor?

How well controlled is your asthma in your opinion? _____very well controlled
_____somewhat controlled
_____not well controlled

How satisfied are you with your asthma care? _____very satisfied
_____somewhat satisfied
_____not satisfied

* These questions are examples and do not represent a standardized assessment instrument. The validity and reliability of these questions have not been assessed.

The exact frequency of clinician visits is a matter of clinical judgment. **Patients with uncontrolled and/or severe persistent asthma and those needing additional supervision to help them follow their treatment plan need to be seen more often.**

Patient Self-Assessment

Self-assessment by the patient and/or family is important to determine from *their* perspective whether the asthma is well controlled. Two methods are recommended: a daily diary (see figure 1-9 for an example) and a periodic self-assessment form to be filled out by the patient and/or family member at the time of the followup visits to the clinician (figure 1-8).

- The daily diary should include the key factors to be monitored at home: symptoms and/or peak flow, medication use, and restricted activity.
- The periodic self-assessment sheet completed at office visits is intended to capture the patient's and family's impression of asthma control, self-management skills, and overall satisfaction with care.

Patients are less likely to see completion of diaries and forms as a burden if they receive feedback from the clinician that allows them to see value in self-monitoring. Monitoring with a daily diary will be most useful to patients whose asthma is not yet under control and who are trying new treatments. It is also useful for those who need help identifying environmental or occupational exposures that make their asthma worse.

Population-Based Assessment

Asthma care is of increasing interest in various health care settings. Important regulatory organizations for the industry (e.g., the National Committee on Quality Assurance) have included the care of persons with asthma as a key indicator of quality of managed care. In this context, periodic population-based assessment of asthma care has begun to emerge as an issue for patients and their clinical providers. This type of assessment often uses population experience, such as hospitalization or emergency department visit rates, to examine care within different clinical settings and among different providers. Complex standardized population surveys (including lengthy health status instruments) are being tested experimentally in the managed care setting.

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COMPONENT 2 :

CONTROL OF FACTORS CONTRIBUTING TO ASTHMA SEVERITY

KEY POINTS

- Exposure of asthma patients to irritants or allergens to which they are sensitive has been shown to increase asthma symptoms and precipitate asthma exacerbations.
- For at least those patients with persistent asthma on daily medications, the clinician should:
 - Identify allergen exposures
 - Use the patient's history to assess sensitivity to seasonal allergens
 - Use skin testing or in vitro testing to assess sensitivity to perennial indoor allergens
 - Assess the significance of positive tests in context of patient's medical history
- Patients with asthma at any level of severity should avoid:
 - Exposure to allergens to which they are sensitive.
 - Exposure to environmental tobacco smoke.
 - Exertion when levels of air pollution are high.
 - Use of beta-blockers.
 - Sulfite-containing and other foods to which they are sensitive.
- Adult patients with severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or nonsteroidal anti-inflammatories should be counseled regarding the risk of severe and even fatal exacerbations from using these drugs.
- Patients should be treated for rhinitis, sinusitis, and gastroesophageal reflux, if present.
- Patients with persistent asthma should be given an annual influenza vaccine.

DIFFERENCES FROM 1991 EXPERT PANEL REPORT

- Skin testing or in vitro testing is now specifically recommended for at least those patients with persistent asthma exposed to perennial indoor allergens.
 - Adult patients with severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or nonsteroidal anti-inflammatories are to be counseled regarding the risk of severe and even fatal exacerbations from using these drugs. In the 1991 report, all asthma patients were recommended to avoid aspirin.
 - Routine use of chemicals to kill house-dust mites and denature the antigen is no longer recommended as a control measure.
 - The discussion of tartrazine sensitivity in the 1991 version was deleted.
 - Annual influenza vaccinations are now specifically recommended for patients with persistent asthma. The recommendation to consider pneumococcal vaccine was deleted.
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For successful long-term asthma management, it is essential to identify and reduce exposures to relevant allergens and irritants and to control other factors that have been shown to increase asthma symptoms and/or precipitate asthma exacerbations. These factors fall into four categories: inhalant allergens, occupational exposures, nonallergic factors, and other factors. Ways to reduce the effects of these factors on asthma are discussed in this component.

- Inhalant allergens:
 - Animal allergens
 - House-dust mites
 - Cockroach allergens
 - Indoor fungi (molds)
 - Outdoor allergens
- Occupational exposures
- Irritants:
 - Tobacco smoke
 - Indoor/outdoor pollution and irritants
- Other factors that can influence asthma severity:
 - Rhinitis/sinusitis
 - Gastroesophageal reflux
 - Sensitivity to aspirin, other nonsteroidal anti-inflammatory drugs, and sulfites
 - Topical and systemic beta-blockers
 - Viral respiratory infections

INHALANT ALLERGENS

Exposure of an asthma patient to inhalant allergens to which the patient is sensitive increases airway inflammation and symptoms. Substantially reducing such exposure will result in significantly reduced inflammation, symptoms, and need for medication (see a summary of the evidence in box 1). In the opinion of the Expert Panel, patients with asthma at any level of severity should be queried about exposures to inhalant allergens.

Diagnosis—Determine Relevant Inhalant Sensitivity

Demonstrating a patient's relevant sensitivity to inhalant allergens will enable the clinician to recommend specific environmental controls to reduce exposures. It will also help the patient understand the pathogenesis of asthma and the value of allergen avoidance. Given the importance of allergens and

BOX 1. THE STRONG ASSOCIATION BETWEEN SENSITIZATION TO ALLERGIES AND ASTHMA: A SUMMARY OF THE EVIDENCE

The association of asthma and allergy has long been recognized. Recent studies confirm that sensitization among genetically susceptible populations to certain indoor allergens such as house-dust mite, animal dander, and cockroach or to the outdoor fungus *Alternaria* is a risk for developing asthma in children (Peat et al. 1993, 1994; Sears et al. 1993a, 1993b; Sporik et al. 1990). Sensitization to outdoor pollens carries less risk for asthma (Sears et al. 1989), although grass (Reid et al. 1986) and ragweed (Creticos et al. 1996) pollen exposure has been associated with seasonal asthma. It is widely accepted that the importance of inhalant sensitivity as a cause of asthma declines with advancing age (Pollart et al. 1989).

An allergic reaction in the airways caused by natural exposure to allergens has been shown to lead to an increase in inflammatory reaction, increased airway hyperresponsiveness (Boulet et al. 1983; Peroni et al. 1994; Piacentini et al. 1993), and increased eosinophils in bronchoalveolar lavage (Rak et al. 1991). Other research has demonstrated that asthma symptoms, pulmonary function, and need for medication in mite-sensitive asthma patients correlate with the level of house-dust mite exposure (Vervloet et al. 1991; Zock et al. 1994) and that reducing house-dust mite exposure reduces asthma symptoms, nonspecific bronchial hyperresponsiveness, and evidence of active inflammation (Peroni et al. 1994; Piacentini et al. 1993; Simon et al. 1994). Inhalant allergen exposure to seasonal outdoor fungal spores (Targonski et al. 1995; O'Hollaren et al. 1991) and to indoor allergens (Call et al. 1994) has also been implicated in fatal exacerbations of asthma. These reports emphasize that allergen exposure must be considered in the treatment of asthma.

The important allergens for children and adults appear to be those that are inhaled. Food allergens are not a common precipitant of asthma symptoms. Foods are an important cause of anaphylaxis in adults and children (Golbert et al. 1969; Sampson et al. 1992), but significant lower respiratory tract symptoms are uncommon even with positive double-blind food challenges (James et al. 1994).

their control to asthma morbidity and asthma management, the Expert Panel recommends that patients with persistent asthma who require daily therapy be evaluated for allergens as possible contributing factors as follows:

1. Determine the patient's exposure to allergens (see relevant questions in figure 2-1).
2. Assess sensitivity to the allergens to which the patient is exposed.
 - Use the patient's medical history, which is usually sufficient, to determine sensitivity to seasonal allergens.
 - Use skin testing or in vitro testing to determine the presence of specific IgE antibodies to the indoor allergens to which the patient is exposed year round (see figure 2-2 for a comparison of skin and in vitro tests). Allergy testing is the only reliable way to determine sensitivity to perennial indoor allergens (see box 2 for further explanation).

(For selected patients with asthma at any level of severity, detection of specific IgE sensitivity to seasonal or perennial allergens may be indicated as a basis for avoidance, for immunotherapy, or to characterize the patient's atopic status.)
3. Assess the clinical significance of positive allergy tests in the context of the patient's medical history (see figure 2-3).

Management—Reduce Exposure

The first and most important step in controlling allergen-induced asthma is to reduce exposure to relevant indoor and outdoor allergens. Effective ways patients can reduce their exposures to indoor and outdoor allergens are discussed below and summarized in figure 2-4, which also addresses irritants. Although these recommendations focus on the home environment, reductions in exposures to allergens and irritants are also appropriate in other environments where the patient spends extended periods of time, such as school, work, or day care. For information about companies that distribute products to help reduce allergen exposure, contact the Asthma and Allergy Foundation of America at 800-727-8462 or the Allergy and Asthma Network/Mothers of Asthmatics at 800-878-4403.

- *Animal Allergens.* All warm-blooded pets, including small rodents and birds, produce dander, urine, feces, and saliva that can cause allergic reactions (Swanson et al. 1985; de Blay et al. 1991a). No studies have been published on the effect of animal allergen avoidance on asthma symptoms; however, based on the opinion of the Expert Panel, the following actions to control animal antigens are recommended:

- If the patient is sensitive, remove the animal and products made of feathers from the home to eliminate exposure.
- If removal of the animal is not acceptable:
 - Keep the pet out of the patient's bedroom.
 - Keep the patient's bedroom door closed. Consider placing dense filtering material over forced air outlets to trap airborne dander particles.
 - Remove upholstered furniture and carpets from the home or isolate the pet from them to the extent possible.

Weekly washing of the pet may decrease the amount of dander and dried saliva the animal contributes to the environment (de Blay et al. 1991b; Klucka et al. 1995).

- *House-Dust Mite Allergen.* House-dust mites are universal in areas of high humidity (most areas of the United States) but are usually not present at high altitudes or in arid areas unless moisture is added to the indoor air. Mites depend on atmospheric moisture and human dander for survival. High levels of mites can be found in dust from mattresses, pillows, carpets, upholstered furniture, bed covers, clothes, and soft toys. The patient's bed is the most important source of dust mites to control. Recommended mite control measures are listed below (Platts-Mills et al. 1982).

Essential actions to control mites include:

- Encase the mattress in an allergen-impermeable cover.
- Encase the pillow in an allergen-impermeable cover or wash it weekly.

FIGURE 2-1. ASSESSMENT QUESTIONS* FOR ENVIRONMENTAL AND OTHER FACTORS THAT CAN MAKE ASTHMA WORSE

Inhalant Allergens

Does the patient have symptoms year round? (If yes, ask the following questions. If no, see next set of questions.)

- Does the patient keep pets indoors? What type?
- Does the patient have moisture or dampness in any room of his or her home (e.g., basement)? (Suggests house-dust mites, molds.)
- Does the patient have mold visible in any part of his or her home? (Suggests molds.)
- Has the patient seen cockroaches in his or her home in the past month? (Suggests significant cockroach exposure.)
- Assume exposure to house-dust mites unless patient lives in a semiarid region. However, if a patient living in a semiarid region uses a swamp cooler, exposure to house dust mites must still be assumed.

Do symptoms get worse at certain times of the year? (If yes, ask when symptoms occur.)

- Early spring? (trees)
- Late spring? (grasses)
- Late summer to autumn? (weeds)
- Summer and fall? (*Alternaria*, *Cladosporium*)

Tobacco Smoke

- Does the patient smoke?
- Does anyone smoke at home or work?
- Does anyone smoke at the child's day care?

Indoor/Outdoor Pollutants and Irritants

- Is a wood-burning stove or fireplace used in the patient's home?
- Are there unvented stoves or heaters in the patient's home?
- Does the patient have contact with other smells or fumes from perfumes, cleaning agents, or sprays?

Workplace Exposures

- Does the patient cough or wheeze during the week, but not on weekends when away from work?
- Do the patient's eyes and nasal passages get irritated soon after arriving at work?
- Do coworkers have similar symptoms?
- What substances are used in the patient's worksite? (Assess for sensitizers.)

Rhinitis

- Does the patient have constant or seasonal nasal congestion and/or postnasal drip?

Gastroesophageal Reflux

- Does the patient have heartburn?
- Does food sometimes come up into the patient's throat?
- Has the patient had coughing, wheezing, or shortness of breath at night in the past 4 weeks?
- Does the infant vomit followed by cough or have wheezy cough at night? Are symptoms worse after feeding?

Sulfite Sensitivity

- Does the patient have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?

Medication Sensitivities and Contraindications

- What medications does the patient use now (prescription and nonprescription)?
- Does the patient use eyedrops? What type?
- Does the patient use any medications that contain beta-blockers?
- Does the patient ever take aspirin or other nonsteroidal anti-inflammatory drugs?
- Has the patient ever had symptoms of asthma after taking any of these medications?

* These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

FIGURE 2-2. COMPARISON OF SKIN TESTS WITH IN VITRO TESTS**Advantages of skin tests:**

- Less expensive than in vitro tests
- Results are available within 1 hour.
- More sensitive than in vitro tests
- Results are visible to the patient.
This may encourage compliance with environmental control measures.

Advantages of RAST and other in vitro tests:

- Do not require knowledge of skin testing technique
- Do not require availability of allergen extracts
- Can be performed on patients who are taking medications that suppress the immediate skin test (antihistamines, antidepressants)
- No risk of systemic reactions
- Can be done for patients with extensive eczema

BOX 2. RATIONALE FOR ALLERGY TESTING FOR PERENNIAL INDOOR ALLERGENS

Determination of sensitivity to a perennial indoor allergen is usually not possible with a patient medical history alone (Murray and Milner 1995). Increased symptoms during vacuuming or bed making and decreased symptoms when away from home on a business trip or vacation are suggestive but not sufficient. Allergy skin or in vitro tests are reliable in determining the presence of specific IgE (Adinoff et al. 1990), but these tests do not determine whether the specific IgE is responsible for the patient's symptoms. That is why patients should only be tested for sensitivity to the allergens to which they are exposed and why the third step in evaluating patients for allergen sensitivity calls for assessing the clinical relevance of the sensitivity.

The recommendation to do skin or in vitro tests for patients with persistent asthma exposed to perennial indoor allergens will result in a limited number of allergy tests for about half of all asthma patients. This is based on the prevalence of persistent asthma and the level of exposure to indoor allergens. It is estimated that about half of all asthma patients have persistent asthma based on data on children in the United States (Taylor and Newacheck 1992) and on adults in Australia (Boston Consulting Group 1992). About 80 percent of the U.S. population is exposed to house-dust mites (Nelson and Fernandez-Caldas 1995), 60 percent to cat or dog, and a much smaller percentage to both animals (Ingram et al. 1995). Cockroaches are a consideration only in the inner city and southern parts of the United States.

Skin or in vitro tests for patients exposed to perennial allergens are essential to justify the expense and effort involved in implementing environmental controls. In addition, patient adherence to maintaining environmental controls (e.g., with regard to pets) is likely to be poor without proof of the patient's sensitivity.

FIGURE 2-3. PATIENT INTERVIEW QUESTIONS* FOR ASSESSING THE CLINICAL SIGNIFICANCE OF POSITIVE ALLERGY TESTS

■ *Animal Dander.* If there are pets in the patient's home and the patient is sensitive to dander of that species of animal, the likelihood that animal dander allergy is contributing to asthma symptoms is increased if answers to the following questions are affirmative. However, absence of positive responses does not exclude a contribution of animal dander to the patient's symptoms.

- Do nasal, eye, or chest symptoms appear in a room where carpets are being or have just been vacuumed?
- Do nasal, eye, or chest symptoms improve when away from home for a week or longer?
- Do the symptoms become worse the first 24 hours after returning home?

■ *House-Dust Mites.* Mite allergy is more likely to be a contributing factor to asthma severity if answers to the following questions are affirmative. However, absence of a positive response does not exclude a contribution of mite allergen to the patient's symptoms.

- Do nasal, eye, or chest symptoms appear in a room where carpets are being or have just been vacuumed?
- Does making a bed cause nasal, eye, or chest symptoms?

■ *Outdoor Allergens (Pollens and Outdoor Molds).* Contribution of pollens and outdoor molds in causing asthma symptoms is suggested by a positive answer to this question:

- Is asthma consistently worse in spring, summer, fall, or parts of the growing season?

Usually, if pollen or mold spores are causing increased asthma symptoms, the patient will also have symptoms of allergic rhinitis—sneezing, itching nose and eyes, runny and obstructed nose.

■ *Indoor Fungi (Molds).* Contribution of indoor molds in causing asthma symptoms is suggested by a positive answer to this question:

- Do nasal, eye, or chest symptoms appear in damp or moldy rooms, such as basements?

* These questions are provided as examples for the clinician. The validity and reliability of these questions have not been assessed.

- Wash the sheets and blankets on the patient's bed weekly in hot water. A temperature of $>130^{\circ}\text{F}$ is necessary for killing house-dust mites.

Desirable actions to control mites include:

- Reduce indoor humidity to less than 50 percent.
- Remove carpets from the bedroom.
- Avoid sleeping or lying on upholstered furniture.
- Remove from the home carpets that are laid on concrete.
- In children's beds, minimize the number of stuffed toys and wash the toys weekly in hot water.

Chemical agents are available for killing mites and denaturing the antigen; however, the effects are not dramatic and do not appear to be maintained for long periods. Therefore, use of these agents in the homes of house-dust mite-sensitive asthma patients should not be recommended routinely (Woodfolk et al. 1995). Vacuuming removes mite allergen from carpets but is inefficient at removing live mites.

■ *Cockroach Allergen.* Cockroach sensitivity and exposure are common among patients with asthma who live in inner cities (Kang et al. 1993; Call et al. 1992). In an inner-city asthma study, asthma severity increased with increasing levels of cockroach antigen in the bedroom of sensitized children (Rosenstreich et al. 1997). Although no studies have been published that report the effect of cockroach reduction on asthma symptoms, it is the opinion of the Expert Panel that control measures need to be instituted when the patient is sensitive to cockroaches and infestation is present in the home. Patients should not leave food or garbage exposed. Poison baits, boric acid, and traps are preferred to chemical agents because the latter can be irritating when inhaled by asthma patients. If chemical agents are used, the home should be well ventilated and the patient should not return to the home until the odor has dissipated.

FIGURE 2-4. SUMMARY OF CONTROL MEASURES FOR ENVIRONMENTAL FACTORS THAT CAN MAKE ASTHMA WORSE

Allergens:

Reduce or eliminate exposure to the allergen(s) the patient is sensitive to, including:

- **Animal dander:** Remove animal from house or, at a minimum, keep animal out of patient's bedroom and seal or cover with a filter air ducts that lead to bedroom.
- **House-dust mites:**
 - **Essential:** Encase mattress in an allergen-impermeable cover; encase pillow in an allergen-impermeable cover or wash it weekly; wash sheets and blankets on the patient's bed in hot water weekly (water temperature of ≥ 130 °F is necessary for killing mites).
 - **Desirable:** Reduce indoor humidity to less than 50 percent; remove carpets from the bedroom; avoid sleeping or lying on upholstered furniture; remove carpets that are laid on concrete.
- **Cockroaches:** Use poison bait or traps to control. Do not leave food or garbage exposed.
- **Pollens (from trees, grass, or weeds) and outdoor molds:** To avoid exposures, adults should stay indoors with windows closed during the season in which they have problems with outdoor allergens, especially during the afternoon.
- **Indoor mold:** Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to less than 50 percent.

Tobacco Smoke:

Advise patients and others in the home who smoke to stop smoking or to smoke outside the home. Discuss ways to reduce exposure to other sources of tobacco smoke, such as from day care providers and the workplace.

Indoor/Outdoor Pollutants and Irritants:

Discuss ways to reduce exposures to the following:

- Wood-burning stoves or fireplaces
- Unvented stoves or heaters
- Other irritants (e.g., perfumes, cleaning agents, sprays)

- **Indoor Fungi (Molds).** Indoor fungi are particularly prominent in humid environments and homes that have dampness problems. Children living in homes with dampness have increased respiratory symptoms (Cuijpers et al. 1995; Verhoeff et al. 1995), but the relative contribution of fungi, house-dust mites, or irritants is not clear. Because an association between indoor fungi and respiratory and allergic disease is suggested by some studies (Bjornsson et al. 1995; Smedje et al. 1996; Strachan 1988), measures to control dampness or fungal growth in the home may be beneficial.
- **Outdoor Allergens (Tree, Grass, and Weed Pollens and Seasonal Mold Spores).** Patients can reduce exposure by staying indoors with windows closed in an air-conditioned environment (Solomon et al. 1980), particularly during the midday and afternoon when pollen and some spore counts are highest (Long and Kramer 1972; Smith and Rooks 1954; Mullins et al. 1986). Conducting outdoor activities shortly after sunrise will result in less pollen exposure. These actions may not be realistic for some patients, especially children.

Immunotherapy

Allergen immunotherapy may be considered for asthma patients when (1) there is clear evidence of a relationship between symptoms and exposure to an unavoidable allergen to which the patient is sensitive, (2) symptoms occur all year or during a major portion of the year, and (3) there is difficulty controlling symptoms with pharmacologic management either because the medication is ineffective, multiple medications are required, or the patient is not accepting of medication. This recommendation is based on the opinion of the Expert Panel and the evidence described below. If use of allergen immunotherapy is elected, it should be administered only in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can, but rarely does, occur (AAAI Board of Directors 1994; Frew 1993). Controlled studies of immunotherapy, usually conducted with single allergens, have demonstrated reduction in asthma symptoms caused by exposure to grass, cat, house-dust mite, ragweed, *Cladosporium*, and *Alternaria* (Reid et al. 1986; Malling et al. 1986; Creticos et al. 1996; Horst et al. 1990). A meta-analysis of 20 randomized, placebo-controlled studies has confirmed the effectiveness of immunotherapy in asthma (Abramson et al. 1995). Few studies have

been reported on multiple allergen mixes, which are commonly employed in clinical practice.

The course of allergen immunotherapy is typically of 3 to 5 years' duration. Reactions to immunotherapy, especially bronchoconstriction, are more frequent among patients with asthma, particularly those with poorly controlled asthma, compared with those with allergic rhinitis (Reid et al. 1993). For this reason, enthusiasm for the use of immunotherapy differs considerably among experts (Abramson et al. 1995; Canadian Society of Allergy and Clinical Immunology 1995; Frew 1993).

Assessment of Devices That May Modify Indoor Air

- **Vacuuming carpets once or twice a week is essential to reduce accumulation of house dust.** Patients sensitive to components of house dust should avoid using conventional vacuum cleaners, and these patients should stay out of rooms where a vacuum cleaner is being or has just been used (Murray et al. 1983). If patients vacuum, they can use a dust mask, a central cleaner with the collecting bag outside the home, or a cleaner fitted with a HEPA (high-efficiency particulate air) filter or with a double bag (Woodfolk et al. 1993).
- **Humidifiers and evaporative (swamp) coolers are not recommended for use in the homes of house-dust mite-sensitive patients with asthma.** These are potentially harmful because increased humidity may encourage the growth of both mold (Solomon 1976) and house-dust mites (Ellingson et al. 1995). In addition, humidifiers may pose a problem if not properly cleaned because they can harbor and aerosolize mold spores (Solomon 1974).
- **Air conditioning during warm weather is recommended for asthma patients** because it allows windows and doors to stay closed, which prevents entry of outdoor allergens (Solomon et al. 1980). Regular use of central air conditioning also will usually control humidity sufficiently to reduce house-dust mite growth (Lintner and Brame 1993).
- **Use of a dehumidifier will reduce house-dust mite levels in areas where the humidity of the outside air remains high for most of the year** (Cabrera et al. 1995).

- **Indoor air-cleaning devices cannot substitute for the more effective measures described previously** (see page 43, Management—Reduce Exposure). However, air-cleaning devices (i.e., HEPA and electrostatic precipitating filters) have been shown to reduce airborne cat dander (de Blay et al. 1991b), mold spores (Maloney et al. 1987), and particulate tobacco smoke (U.S. Environmental Protection Agency 1990). Air cleaners cannot significantly reduce exposure to house-dust mite and cockroach allergens because these heavy particles do not remain airborne (de Blay et al. 1991a). Most studies of air cleaners have failed to demonstrate an effect on asthma symptoms or pulmonary function (Nelson et al. 1988; Reisman et al. 1990; Warner et al. 1993; Warburton et al. 1994).

- **Air-duct cleaning of heating/ventilation/air conditioning systems has been reported to decrease levels of airborne fungi in residences** (Garrison et al. 1993). The effect on levels of house-dust mite or animal dander has not been studied. Limited evidence precludes the Expert Panel from making a recommendation in this area.

OCCUPATIONAL EXPOSURES

Early recognition and control of exposures are particularly important in occupationally induced asthma, because the likelihood of complete resolution of symptoms decreases with time (Chan-Yeung et al. 1987; Pisati et al. 1993). Occupational asthma is suggested by a correlation between asthma symptoms and work, with improvement when away from work for several days. Other indications of workplace exposure are listed in figure 2-5. The patient may fail to recognize the work relationship, because symptoms often begin several hours after exposure. Serial peak flow records at work and away from work can confirm the work association (Moscato et al. 1995).

Workplace exposure to sensitizing chemicals or dusts can induce asthma, which often persists after the exposures are terminated (Chan-Yeung et al. 1987; Pisati et al. 1993). This should be distinguished from allergen- or irritant-induced aggravation of preexisting asthma. Acute exposure to irritant gases, dusts, or fumes can cause an asthma-like condition (reactive airway dysfunction syndrome) (Brooks et al. 1985).

Patient confidentiality issues are particularly important in work-related asthma. Because even general

inquiries about the potential adverse health effects of work exposures may occasionally result in reprisals against the patient (e.g., job loss), asthma patients need to be informed of this possibility and be full partners in the decision to approach management regarding the effects or control of workplace exposures.

IRRITANTS

In the opinion of the Expert Panel, patients with asthma at any level of severity should be queried about exposures to irritants. Sample assessment questions are in figure 2-1.

Environmental Tobacco Smoke

Asthma patients should not smoke or be exposed to environmental tobacco smoke (Marquette et al. 1992). Tobacco smoke is the most important environmental indoor irritant and is a major precipitant of asthma symptoms in children and adults (Abbey et al. 1993; Greer et al. 1993; Jindal et al. 1994; Leuenberger et al. 1994). Jindal and colleagues (1994) found that exposure of adults to environmental tobacco smoke is associated with decreased levels of pulmonary function, increased requirements for medication, and more frequent absences from work. In addition, exposure to maternal smoke has been shown to be a risk factor for the development of asthma in infancy (Arshad and Hide 1992) and childhood (Frischer et al. 1992; Schmitzberger et al. 1993; Gortmaker et al. 1982; Henderson et al. 1995; Soyseth et al. 1995; Martinez et al. 1995; Agudo et al. 1994), although not for persistence of childhood asthma into adulthood (Roorda et al. 1993).

Indoor/Outdoor Air Pollution and Irritants

Asthma patients should avoid exertion or exercise outside to the extent possible when levels of air pollution are high. Increased pollution levels, particularly of respirable particulates (Abbey et al. 1993; Koenig et al. 1993; Pope et al. 1991; Walters et al. 1994; Schwartz et al. 1993; Ostro et al. 1995) and ozone (Abbey et al. 1993; Cody et al. 1992; Ponka 1991; Thurston et al. 1992; Ostro et al. 1995; Romieu et al. 1995; Kesten et al. 1995; White et al. 1994), but also of SO₂ (Moseholm et al. 1993) and NO₂ (Moseholm et al. 1993; Kesten et al. 1995), have been reported to precipitate symptoms of asthma (Abbey et al. 1993; Koenig et al. 1987; Moseholm et al. 1993; Pope et al. 1991) and to increase emergency department visits and hospitaliza-

FIGURE 2-5. EVALUATION AND MANAGEMENT OF WORK-AGGRAVATED ASTHMA AND OCCUPATIONAL ASTHMA

Evaluation

Potential for workplace-related symptoms:

- Recognized sensitizers (e.g., isocyanates, plant or animal products).
- Irritants* or physical stimuli (e.g., cold/heat, dust, humidity).
- Coworkers may have similar symptoms.

Patterns of symptoms (in relation to work exposures):

- Improvement during vacations or days off (may take a week or more).
- Symptoms may be immediate (<1 hour), delayed (most commonly, 2 to 8 hours after exposure), or nocturnal.
- Initial symptoms may occur after high-level exposure (e.g., spill).

Documentation of work-relatedness of airflow limitation:

- Serial charting for 2 to 3 weeks (2 weeks at work and up to 1 week off work as needed to identify or exclude work-related changes in peak expiratory flow):
 - Record when symptoms and exposures occur.
 - Record when a bronchodilator is used.
 - Measure and record peak flow every 2 hours while awake.
- Immunologic tests.
- Referral for further confirmatory evaluation (e.g., bronchial challenges).

Management

Work-aggravated asthma:

- Work with onsite health care providers or managers/supervisors.
- Discuss avoidance, ventilation, respiratory protection, tobacco smoke-free environment.

Occupationally induced asthma:

- Recommend complete cessation of exposure to initiating agent.

* Material Safety Data Sheets may be helpful for identifying respiratory irritants, but many sensitizers are not listed.

tions for asthma (Walters et al. 1994; Schwartz et al. 1993; Cody et al. 1992; Ponka 1991; Thurston et al. 1992; Romieu et al. 1995; Kesten et al. 1995; White et al. 1994).

Patients also should avoid exposure to fumes from unvented gas, oil, or kerosene stoves; wood-burning appliances or fireplaces (Ostro et al. 1994); sprays; and strong odors because they irritate the lungs and can precipitate asthma symptoms.

OTHER FACTORS THAT CAN INFLUENCE ASTHMA SEVERITY

Rhinitis/Sinusitis

Treatment of upper respiratory tract symptoms is an integral part of asthma management. Intranasal corticosteroids are recommended for the treatment of chronic rhinitis in patients with persistent asthma. Antihistamine/decongestant combinations also may be used; they provide symptomatic relief but have not been shown to have a protective effect on the lower airways secondary to their action on the nose. Intranasal corticosteroids reduce nasal inflammation, obstruction, and discharge and have been shown to reduce lower airway hyperresponsiveness and asthma symptoms (Aubier et al. 1992; Watson et al. 1993; Corren et al. 1992; Welsh et al. 1987). Intranasal cromolyn has been shown to reduce symptoms of asthma during the ragweed season, but to a lesser extent than intranasal corticosteroids in the same study (Welsh et al. 1987).

Treatment of sinusitis includes medical measures to promote drainage (Zeiger 1992) and the use of antibiotics when complicating acute bacterial infection is present (Wald 1992; Gwaltney et al. 1992). In cases of subacute or chronic sinusitis, physicians need to make a judgment regarding the appropriateness of antibiotic therapy. Antibiotic therapy was not shown to be of clear benefit in children who had nasal symptoms or cough for longer than 3 weeks and who had abnormal sinus x rays but no fever (Dohlman et al. 1993).

Asthma is commonly associated with perennial and seasonal rhinitis and sinusitis. Studies indicate that inflammation of the upper airway contributes to lower airway hyperresponsiveness and asthma symptoms (Watson et al. 1993; Corren et al. 1992; Welsh et al. 1987). The histopathology in the chronically thickened mucosa of the paranasal sinuses is similar to

that in the nose and bronchi, with a primarily eosinophilic infiltrate that, in most patients, is notably lacking in neutrophils (Harlin et al. 1988; Demoly et al. 1994).

Gastroesophageal Reflux

Medical management of gastroesophageal reflux should be instituted for any patients with asthma complaining of frequent heartburn or pyrosis, particularly those with frequent episodes of nocturnal asthma. Medical management of gastroesophageal reflux includes:

- Avoiding food and drink within 3 hours of retiring (Nelson 1984)
- Elevating the head of the bed on 6- to 8-inch blocks (Nelson 1984)
- Using appropriate pharmacologic therapy (Hixson et al. 1992)

For patients who have persistent symptoms following optimal therapy, further evaluation is indicated.

For patients with poorly controlled asthma, particularly with a nocturnal component, investigation for gastroesophageal reflux may be warranted even in the absence of suggestive symptoms (Irwin et al. 1989).

The symptoms of gastroesophageal reflux are common in both children and adults with asthma (Nelson 1984). Reflux during sleep can contribute to nocturnal asthma (Martin et al. 1982; Davis et al. 1983). Both medical (Ekstrom et al. 1989) and surgical (Perrin-Fayolle et al. 1989) therapy of gastroesophageal reflux have been reported to reduce the symptoms of asthma.

Aspirin Sensitivity

Adult patients with asthma should be questioned regarding precipitation of bronchoconstriction by aspirin and other nonsteroidal anti-inflammatory drugs. If they have experienced a reaction to any of these drugs, they should be informed of the potential for all these drugs to precipitate severe and even fatal exacerbations. Adult patients with severe persistent asthma or nasal polyps should be counseled regarding the risk of using these drugs. Usually safe alternatives to aspirin include acetaminophen or salsalate (Szczeklik et al. 1977; Settipane et al. 1995).

From 3 percent of patients with asthma seen in a private allergy practice (Chafee and Settiple 1974) to 39 percent of adults with asthma admitted to an asthma referral hospital (Spector et al. 1979) have been reported to experience severe and even fatal exacerbations of asthma after taking aspirin or certain other nonsteroidal anti-inflammatory drugs. The prevalence of aspirin sensitivity increases with increasing age and severity of asthma (Chafee and Settiple 1974; Spector et al. 1979).

Sulfite Sensitivity

Patients who have asthma symptoms associated with eating processed potatoes, shrimp, or dried fruit or with drinking beer or wine should avoid these products (Taylor et al. 1988). These products contain sulfites, which are used to preserve foods and beverages. They have caused severe asthma exacerbations, particularly in patients with severe persistent asthma.

Beta-Blockers

Nonselective beta-blockers, including those in ophthalmological preparations, can cause asthma symptoms and should be avoided by asthma patients (Odeh et al. 1991; Schoene et al. 1984), although cardioselective beta-blockers, such as betaxolol, may be tolerated (Dunn et al. 1986).

Infections

Annual influenza vaccinations are recommended for patients with persistent asthma (Bell et al. 1978; CDC 1993). It is well established that viral respiratory infections can exacerbate asthma, particularly in children with asthma under the age of 10 (Busse et al. 1993). Respiratory syncytial virus, rhinovirus, and influenza virus have been implicated (Busse et al. 1993), with rhinovirus being implicated in the majority of the exacerbations of asthma in children (Johnston et al. 1995). The role of infections causing exacerbations of asthma also appears to be important in adults (Nicholson et al. 1993).

Viral infections are the most frequent precipitants of asthma exacerbations in infancy. In the majority of cases, young children are predisposed to have bronchial obstruction during viral infections because of very small airway size (Martinez et al. 1995) and will not have further exacerbations after infancy.

However, chronic asthma also may start as early as the first year of life among infants with a family history of asthma, persistent rhinorrhea, atopic dermatitis, or high IgE levels. Early identification of these infants allows institution of environmental controls to reduce exposure to tobacco smoke, animal dander, and house-dust mites.

PREVENTING THE ONSET OF ASTHMA

Primary prevention of asthma (preventing initial development) is an accepted approach for occupational asthma (Venables 1994; Chan-Yeung et al. 1987) but remains unproven outside the workplace. Recent studies indicate that exposures to high levels of house-dust mite antigen (Sporik et al. 1990; Peat et al. 1993, 1994) and environmental tobacco smoke (Martinez et al. 1995; Kuehr et al. 1995) are associated with an increased incidence of asthma among infants. This suggests that reducing these exposures may result in reduction in the incidence of asthma. Prolonged breast feeding and avoidance of early introduction of allergenic foods have been reported to reduce eczema and food sensitization but not to reduce the prevalence of asthma (Zeiger 1994).

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COMPONENT 3 : PHARMACOLOGIC THERAPY

KEY POINTS

- Underdiagnosis and inappropriate therapy are major contributors to asthma morbidity and mortality.
- Goals of asthma therapy are:
 - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
 - Maintain (near) "normal" pulmonary function
 - Maintain normal activity levels (including exercise and other physical activity)
 - Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
 - Provide optimal pharmacotherapy with minimal or no adverse effects
 - Meet patients' and families' expectations of and satisfaction with asthma care
- Persistent asthma is most effectively controlled with daily anti-inflammatory therapy.
- A stepwise approach to pharmacologic therapy is recommended:
 - The amount and frequency of medication is dictated by asthma severity and directed toward suppression of increasing airway inflammation.
 - Initiate therapy at a higher level at the onset to establish prompt control and then step down.
 - Continual monitoring is essential to ensure that asthma control is achieved.
 - Step down therapy cautiously once control is achieved and sustained.
 - Step-down therapy is necessary to identify the minimum medication necessary to maintain control.
- Regular followup visits (at 1- to 6-month intervals) are essential to maintain control and consider appropriate step down in therapy.
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal asthma control.
- At each step, patients should be advised to avoid or control allergens, irritants, or other factors that make the patient's asthma worse.
- Referral to an asthma specialist for consultation or comanagement is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be considered for patients who require step 3 care. For patients younger than 3 years of age, referral is *recommended* if the patient requires step 3 or 4 care and should be *considered* if the patient requires step 2 care.
- New medications are available.
 - Long-acting inhaled beta₂-agonists
 - Effective 12-hour bronchodilator
 - Adjunctive therapy to inhaled corticosteroids for maintaining control, especially helpful for nighttime symptoms
 - Not to be used to treat acute symptoms or exacerbations
 - Nedocromil
 - Similar role in therapy as cromolyn sodium, with similar safety profile
 - Leukotriene modifiers
 - Zafirlukast, leukotriene receptor antagonist, and zileuton, 5-lipoxygenase inhibitor
 - May be considered alternative daily long-term-control medications for patients with mild persistent asthma who are 12 years of age and older, but further clinical experience and study are needed to establish their roles in therapy

- Increased understanding of inhaled corticosteroids notes that:
 - Inhaled corticosteroids are the most potent inhaled anti-inflammatory agent currently available.
 - Early intervention with inhaled corticosteroids can improve asthma control and normalize lung function and may prevent irreversible airway injury.
 - Higher doses of inhaled corticosteroids may be associated with possible, but not predictable, growth retardation in children. The clinical significance of this potential systemic effect has yet to be determined.
 - Issues regarding clinical comparability and bioavailability of different preparations and different delivery systems indicate the need to adjust doses accordingly.
- Management of asthma exacerbations includes:
 - Inhaled beta₂-agonist to provide prompt relief of airflow obstruction
 - Systemic corticosteroid, for moderate-to-severe exacerbations, to suppress and reverse airway inflammation
 - Oxygen to relieve hypoxia for moderate-to-severe exacerbations
 - Monitoring response to therapy with serial measurements of lung function

DIFFERENCES FROM 1991 EXPERT PANEL REPORT

- Medications are now categorized into two general classes: long-term-control medications used to achieve and maintain control of persistent asthma and quick-relief medications used to treat acute symptoms and exacerbations. *However, the updated report continues to emphasize that the most effective medications for long-term therapy are those shown to have anti-inflammatory effects.*
 - New medications are available—long-acting inhaled beta₂-agonists, nedocromil, zafirlukast, and zileuton—that have positions in therapy for long-term control and prevention of symptoms.
 - There is an increased understanding of inhaled corticosteroids and their significant role in asthma therapy. An estimated clinical comparability of different inhaled corticosteroid preparations is presented.
 - The stepwise approach to asthma therapy emphasizes initiating higher level therapy at the onset to establish prompt control and then stepping down.
 - A new section on asthma in infants and young children incorporates recent studies on wheezing in early childhood.
-

Selecting the appropriate pharmacologic therapy to achieve and maintain control of asthma involves several considerations: the medications and their routes of administration, a stepwise approach to managing asthma long term as a chronic disorder, and a protocol for managing exacerbations. Each will be discussed in this component. In addition, substantial reports in the literature since publication of the 1991 Expert Panel Report have commented on the safety of regular administration of inhaled beta₂-agonists and the potential adverse effects of inhaled corticosteroids. Because of the importance of these

two classes of compounds in the treatment of asthma, it is the opinion of the Panel that special emphasis should be given to these issues. A summary is presented in this component.

The therapeutic strategies provided in this component should be considered in concert with the clinician-patient partnership strategies provided in component 4. Effective communication with, and education of, patients will increase the benefits of the therapeutic regimen.

Pharmacologic Therapy: The Medications

KEY POINTS: THE MEDICATIONS

Long-term-control medications

- **Corticosteroids:** Most potent and effective anti-inflammatory medication currently available. Inhaled form is used in the long-term control of asthma. Systemic corticosteroids are often used to gain prompt control of the disease when initiating long-term therapy.
- **Cromolyn sodium and nedocromil:** Mild-to-moderate anti-inflammatory medications. May be used as initial choice for long-term-control therapy for children. Can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.
- **Long-acting beta₂-agonists:** Long-acting bronchodilator used concomitantly with anti-inflammatory medications for long-term control of symptoms, especially nocturnal symptoms. Also prevents exercise-induced bronchospasm (EIB).
- **Methylxanthines:** Sustained-release theophylline is a mild-to-moderate bronchodilator used principally as adjuvant to inhaled corticosteroids for prevention of nocturnal asthma symptoms. May have mild anti-inflammatory effect.
- **Leukotriene modifiers:** Zafirlukast, a leukotriene receptor antagonist, or zileuton, a 5-lipoxygenase inhibitor, may be considered an alternative therapy to low doses of inhaled corticosteroids or cromolyn or nedocromil for patients >12 years of age with mild persistent asthma, although further clinical experience and study are needed to establish their roles in asthma therapy.

Quick-relief medications

- **Short-acting beta₂-agonists:** Therapy of choice for relief of acute symptoms and prevention of EIB.
- **Anticholinergics:** Ipratropium bromide may provide some additive benefit to inhaled beta₂-agonists in severe exacerbations. May be an alternative bronchodilator for patients who do not tolerate inhaled beta₂-agonists.
- **Systemic corticosteroids:** Used for moderate-to-severe exacerbations to speed recovery and prevent recurrence of exacerbations.

OVERVIEW OF THE MEDICATIONS

Pharmacologic therapy is used to prevent and control asthma symptoms, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. Recommendations in this component reflect the scientific concept that asthma is a chronic disorder with recurrent episodes of airflow limitation, mucus production, and cough. Asthma medications are thus categorized into two general classes: *long-term-control* medications taken daily on a long-term basis to achieve and maintain control of persistent asthma (these medications are also known as long-term preventive, controller, or maintenance medications) and *quick-relief* medications taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction (these medications are also known as reliever or acute rescue medications). Patients with persistent asthma require both classes of medication. Figures 3-1 and 3-2 present summaries of the indications, mechanisms, potential adverse effects, and therapeutic issues for currently available long-term-control and quick-relief medications.

Long-Term-Control Medications

Long-term-control medications are taken daily on a long-term basis to achieve and maintain control of persistent asthma. They include anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers. Because eosinophilic inflammation is a constant feature of the mucosa of the airways in asthma, the most effective long-term-control medications are those that attenuate inflammation (Haahtela et al. 1991; Kerrebijn et al. 1987; van Essen-Zandvliet et al. 1992). The Expert Panel defines anti-inflammatory medications as those that cause a reduction in the markers of airway inflammation in airway tissue or airway secretions (e.g., eosinophils, mast cells, activated lymphocytes, macrophages, and cytokines; or eosinophilic cationic protein and tryptase; or extravascular leakage of albumin, fibrinogen, or other vascular protein) and thus decrease the intensity of airway hyperresponsiveness. Because many factors contribute to the inflammatory response in asthma, many

drugs may be considered anti-inflammatory. It is not yet established, however, which anti-inflammatory actions are responsible for therapeutic effects, such as reduction in symptoms, improvement in expiratory flow, reduction in airway hyperresponsiveness, prevention of exacerbations, or prevention of airway wall remodeling.

Corticosteroids

Corticosteroids are the most potent and consistently effective long-term-control medication for asthma. Their broad action on the inflammatory process may account for their efficacy as preventive therapy. Their clinical effects include reduction in severity of symptoms, improvement in peak expiratory flow and spirometry, diminished airway hyperresponsiveness, prevention of exacerbations, and possibly the prevention of airway wall remodeling (Barnes et al. 1993; Jeffery et al. 1992; Dahl et al. 1993; Fabbri et al. 1993; Gustafsson et al. 1993; Haahtela et al. 1991; Kamada et al. 1996; Rafferty et al. 1985; van Essen-Zandvliet et al. 1992). Which of these clinical effects depend on specific anti-inflammatory actions of corticosteroids is not yet clear. Corticosteroids suppress the generation of cytokines, recruitment of airway eosinophils, and release of inflammatory mediators. These anti-inflammatory actions of corticosteroids have been noted in clinical trials and analyses of airway histology (Busse 1993; Booth et al. 1995; Laitinen et al. 1992; Djukanovic et al. 1992; Duddridge et al. 1993; Laitinen et al. 1991; Levy et al. 1995; McGill et al. 1995).

Dosages for inhaled corticosteroids vary depending upon the specific product and delivery devices (see figure 3-5b). For many patients, a twice-a-day dosing schedule maintains control of asthma; even high doses of some preparations are effective when given twice a day (Noonan et al. 1995). Some studies show that once-daily dosing is effective in mild persistent asthma (Jones et al. 1994; Pincus et al. 1995).

Cromolyn Sodium and Nedocromil

Although cromolyn and nedocromil have distinct properties (Clark 1993), they have similar anti-inflammatory actions. Their mechanism appears to involve the blockade of chloride channels (Alton and Norris 1996), and they modulate mast cell mediator release and eosinophil recruitment (Eady 1986). They also inhibit the early and late asthmatic response to allergen challenge and exercise-induced bronchospasm

(EIB) (Novembre et al. 1994; Alton and Norris 1996; Thompson 1989; Gonzalez and Brogden 1987).

The two compounds are equally effective against allergen challenge (Gonzalez and Brogden 1987), although nedocromil appears to be more potent than cromolyn in inhibiting bronchospasm provoked by exercise (Novembre et al. 1995; deBenedictis et al. 1995), by cold dry air (Juniper et al. 1987), and by bradykinin aerosol (Dixon and Barnes 1989).

Both compounds have been shown to reduce asthma symptoms, improve morning peak flow, and reduce need for quick-relief beta₂-agonists (Lal et al. 1993; Schwartz et al. 1996). Two large clinical trials comparing nedocromil MDI 4 mg qid to cromolyn MDI 2 mg qid demonstrated that they are generally comparable in mild allergic patients and that nedocromil was more effective than cromolyn in nonallergic patients using inhaled corticosteroids. Furthermore, nedocromil may have a modest effect in helping reduce the dose requirements for inhaled corticosteroids (Lal et al. 1993; O'Hickey and Rees 1994; Svendsen and Jørgensen 1991), although some studies did not demonstrate this effect (Wong et al. 1993).

Dosing recommendations for both drugs are for administration four times a day, although nedocromil has been shown to be clinically effective with twice-daily dosing (Creticos et al. 1995).

The clinical response to cromolyn and nedocromil is less predictable than the response to inhaled corticosteroids. Both compounds have a strong safety profile.

Long-Acting Beta₂-Agonists (Beta-Adrenergic Agonists)

The principal action of beta₂-agonists is to relax airway smooth muscle by stimulating beta₂-receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Long-acting inhaled beta₂-agonists have a duration of bronchodilation of at least 12 hours after a single dose (Becker and Simons 1989; D'Alonzo et al. 1994). This class of medication is *not* to be used for exacerbations. Rather, it is used as an adjunct to anti-inflammatory therapy for providing long-term control of symptoms, especially nocturnal symptoms (Yates et al. 1995) and to prevent exercise-induced bronchospasm. The use and safety of beta₂-agonists are discussed on page 67, Special Issues Regarding Safety.

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
<p>Corticosteroids (Glucocorticoids)</p> <p><i>Inhaled:</i> Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Triamcinolone acetonide</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ■ Reduce need for oral corticosteroid. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Anti-inflammatory. Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ■ Reverse β_2-receptor down-regulation. Inhibit microvascular leakage. 	<ul style="list-style-type: none"> ■ Cough, dysphonia, oral thrush (candidiasis). ■ In high doses (see figure 3-5b), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, growth suppression, and skin thinning and easy bruising) (Barnes and Pedersen 1993; Kamada et al. 1996). 	<ul style="list-style-type: none"> ■ Spacer/holding chamber devices and mouth washing after inhalation decrease local side effects and systemic absorption. ■ Preparations are not absolutely interchangeable on a mcg or per puff basis (see figure 3-5c for estimated clinical comparability). New delivery devices may provide greater delivery to airways, which may affect dose. ■ The risks of uncontrolled asthma should be weighed against the limited risks of inhaled corticosteroids. The potential but small risk of adverse events is well balanced by their efficacy. (See text.) ■ Dexamethasone is not included because it is highly absorbed and has long-term suppressive side effects.
<p><i>Systemic:</i> Methylprednisolone Prednisolone Prednisone</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ For short-term (3–10 days) "burst": to gain prompt control of inadequately controlled persistent asthma. ■ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Same as inhaled. 	<ul style="list-style-type: none"> ■ Short-term use: reversible, abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur. ■ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, and <i>Strongyloides</i>. 	<p>Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning (Beam et al. 1992).</p>

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Cromolyn Sodium and Nedocromil	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term prevention of symptoms; may modify inflammation. ■ Preventive treatment prior to exposure to exercise or known allergen. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Anti-inflammatory. Block early and late reaction to allergen. Interfere with chloride channel function. Stabilize mast cell membranes and inhibit activation and release of mediators from eosinophils and epithelial cells. ■ Inhibit acute response to exercise, cold dry air, and SO₂. 	15 to 20 percent of patients complain of an unpleasant taste from nedocromil.	<ul style="list-style-type: none"> ■ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. ■ Dose of cromolyn MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients ■ Safety is the primary advantage of these agents.
<p>Long-Acting Beta₂-Agonists</p> <p><i>Inhaled:</i> Salmeterol</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term prevention of symptoms, especially nocturnal symptoms, added to anti-inflammatory therapy ■ Prevention of exercise-induced bronchospasm. ■ <i>Not to be used to treat acute symptoms or exacerbations.</i> <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Bronchodilation. Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. ■ In vitro, inhibit mast cell mediator release, decrease vascular permeability, and increase mucociliary clearance. ■ Compared to short-acting inhaled beta₂-agonist, salmeterol (but not formoterol) has slower onset of action (15 to 30 minutes) but longer duration (>12 hours). 	<ul style="list-style-type: none"> ■ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QT_c interval in overdose. ■ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ■ See text for additional discussion. 	<ul style="list-style-type: none"> ■ Not to be used to treat acute symptoms or exacerbations. ■ Clinical significance of potentially developing tolerance is uncertain because studies show symptom control and bronchodilation are maintained. ■ Should not be used in place of anti-inflammatory therapy. ■ May provide more effective symptom control when added to standard doses of inhaled corticosteroid compared to increasing the corticosteroid dosage.
<p><i>Oral:</i> Albuterol, sustained-release</p>			<ul style="list-style-type: none"> ■ <i>Inhaled long-acting beta₂-agonists are preferred because they are longer acting and have fewer side effects than oral sustained-release agents.</i>

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
<p>Methylxanthines</p> <p>Theophylline, sustained-release tablets and capsules</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term control and prevention of symptoms, especially nocturnal symptoms. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Bronchodilation. Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism ■ May affect eosinophilic infiltration into bronchial mucosa as well as decrease T-lymphocyte numbers in epithelium. ■ Increases diaphragm contractility and mucociliary clearance. 	<ul style="list-style-type: none"> ■ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ■ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males with prostatism. 	<ul style="list-style-type: none"> ■ Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors (see figure 3-5a), which can produce significant changes in steady-state serum theophylline concentrations. ■ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of inhaled beta₂-agonists. Serum concentration monitoring is mandatory.
<p>Leukotriene Modifiers</p> <p>Zafirlukast tablets</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Leukotriene receptor antagonist; selective competitive inhibitor of LTD₄ and LTE₄ receptors. 	<ul style="list-style-type: none"> ■ No specific adverse effects to date. As with any new drug, there is possibility of rare hypersensitivity or idiosyncratic reactions that cannot usually be detected in initial premarketing trials. One reported case of reversible hepatitis and hyperbilirubinemia; high concentrations may develop in patients with liver impairment. 	<ul style="list-style-type: none"> ■ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Inhibits the metabolism of warfarin and increases prothrombin time; it is a competitive inhibitor of the CYP2C9 hepatic microsomal isozymes. (It has not affected elimination of terfenadine, theophylline, or ethinyl estradiol drugs metabolized by the CYP3A4 isozymes.)
<p>Zileuton tablets</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ 5-lipoxygenase inhibitor. 	<ul style="list-style-type: none"> ■ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia. 	<ul style="list-style-type: none"> ■ Zileuton is microsomal CYP3A4 enzyme inhibitor that can inhibit the metabolism of terfenadine, warfarin, and theophylline. Doses of these drugs should be monitored accordingly. ■ Monitor hepatic enzymes (ALT).

FIGURE 3-2. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
<p>Short-Acting Inhaled Beta₂-Agonists</p> <p>Albuterol Bitolterol Pirbuterol Terbutaline</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Relief of acute symptoms; quick-relief medication. ■ Preventive treatment prior to exercise for exercise-induced bronchospasm. <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Bronchodilation. Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. 	<p>Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.</p>	<ul style="list-style-type: none"> ■ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta₂-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Albuterol liquid is not recommended. ■ For patients with mild intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control (Drazen et al. 1996). Regularly scheduled daily use is not generally recommended. ■ Increasing use or lack of expected effect indicates inadequate asthma control. >1 canister a month (e.g., albuterol-200 puffs per canister) may indicate overreliance on this drug; ≥2 canisters in 1 month poses additional adverse risks. ■ For patients frequently using beta₂-agonist, anti-inflammatory medication should be initiated or intensified.
<p>Anticholinergics</p> <p>Ipratropium bromide</p>	<p><i>Indications</i></p> <ul style="list-style-type: none"> ■ Relief of acute bronchospasm (see Therapeutic Issues column). <p><i>Mechanisms</i></p> <ul style="list-style-type: none"> ■ Bronchodilation. Competitive inhibition of muscarinic cholinergic receptors. ■ Reduces intrinsic vagal tone to the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. ■ May decrease mucus gland secretion. 	<p>Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes.</p>	<ul style="list-style-type: none"> ■ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block exercise-induced bronchospasm. ■ May provide additive effects to beta₂-agonist but has slower onset of action. ■ Is an alternative for patients with intolerance to beta₂-agonists. ■ Treatment of choice for bronchospasm due to beta-blocker medication.

FIGURE 3-2. QUICK-RELIEF MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Corticosteroids	<i>Indications</i>		
<i>Systemic:</i>	<ul style="list-style-type: none"> For moderate-to-severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. 	<ul style="list-style-type: none"> Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur. 	<ul style="list-style-type: none"> Short-term therapy should continue until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3 to 10 days but may require longer.
Methylprednisolone Prednisolone Prednisone	<i>Mechanisms</i>	<ul style="list-style-type: none"> Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, and <i>Strongyloides</i>. 	<ul style="list-style-type: none"> There is no evidence that tapering the dose following improvement prevents relapse.
	<ul style="list-style-type: none"> Anti-inflammatory. See figure 3-1. 		

Methylxanthines

Theophylline, the principally used methylxanthine, provides mild-to-moderate bronchodilation in asthma. Although its mechanism of action has yet to be established (Weinberger and Hendeles 1996; Hendeles et al. 1995), recent evidence suggests that low serum concentrations of theophylline are mildly anti-inflammatory (Sullivan et al. 1994; Kidney et al. 1995; Pauwels 1989). Sustained-release theophylline's main use is as adjuvant therapy, and it is particularly effective for controlling nocturnal asthma symptoms. Sustained-release theophylline may be considered as an alternative, but not preferred, long-term preventive therapy when issues arise concerning cost or adherence to regimens using inhaled medication. Monitoring serum concentration levels is essential to ensure that therapeutic, but not toxic, doses are achieved.

Leukotriene Modifiers

Leukotrienes are potent biochemical mediators released from mast cells, eosinophils, and basophils that contract airway smooth muscle, increase vascular permeability, increase mucus secretions, and attract and activate inflammatory cells in the airways of patients with asthma (Henderson 1994). Two leukotriene modifiers—zafirlukast and zileuton—

have recently become available as oral tablets for the treatment of asthma.

From the information currently available, it appears that leukotriene modifiers improve lung function (Gaddy et al. 1992) and diminish symptoms and the need for short-acting inhaled beta₂-agonists. The majority of trials have been conducted in mild-to-moderate asthma, and the improvements noted have been modest. Leukotriene modifiers may be considered an alternative to low-dose inhaled corticosteroid therapy for patients with mild persistent asthma, although increased clinical experience and further study in a wide range of patients are needed to determine those patients most likely to benefit from leukotriene modifiers and to establish a more specific role for leukotriene modifiers in asthma therapy.

Zafirlukast, a leukotriene receptor antagonist, has been demonstrated to attenuate the late response to inhaled allergen and post-allergen induced bronchial responsiveness (Dahlen et al. 1994; Taylor et al. 1991). Studies comparing zafirlukast to placebo in patients with mild-to-moderate asthma demonstrated that patients treated with zafirlukast experienced modest improvement in FEV₁ (mean improvement of 11 percent above placebo), improved symptom scores, and reduced albuterol use (average decline of 1 puff/day) (Spector et al. 1994). In a small study of healthy

males, 60 mg a day of zafirlukast caused a significant increase in the half-life of warfarin. Consequently, for those individuals receiving zafirlukast and warfarin, it will be necessary to closely monitor prothrombin times and adjust doses of warfarin accordingly.

Zileuton, a 5-lipoxygenase inhibitor, has been demonstrated to provide immediate and sustained improvements in FEV₁ (mean increase of 15 percent above placebo) in placebo-controlled trials in patients with mild-to-moderate asthma (Israel et al. 1993, 1996). Compared to placebo, the patients with moderate asthma treated with zileuton experienced significantly fewer exacerbations requiring oral corticosteroids (Israel et al. 1996), thus suggesting anti-inflammatory action. Finally, zileuton is capable of attenuating bronchoconstriction from exercise (Meltzer et al. 1996) and from aspirin in aspirin-sensitive individuals (Israel et al. 1993). Because liver toxicity has been found in some subjects receiving zileuton, it is recommended that hepatic enzymes (ALT) be monitored in patients who take this medication. Zileuton is a microsomal CYP3A4 enzyme inhibitor that can inhibit the metabolism of terfenadine, warfarin, and theophylline. Doses of these drugs should be monitored accordingly.

Quick-Relief Medications

Quick-relief medications are used to provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. They include short-acting beta₂-agonists and anticholinergics. Although the onset of action is slow (>4 hours), systemic corticosteroids are important in the treatment of moderate-to-severe exacerbations because they prevent progression of the exacerbation, speed recovery, and prevent early relapses.

Short-Acting Beta₂-Agonists

Short-acting beta₂-agonists relax airway smooth muscle and cause a prompt (within 30 minutes) increase in airflow. Inhaled short-acting beta₂-agonists are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB. Concerns about the safety of short-acting beta₂-agonists are discussed in another section of this component (see page 67, Special Issues Regarding Safety).

Anticholinergics

Cholinergic innervation is an important factor in the regulation of airway smooth muscle tone. Ipratropium bromide is a quaternary derivative of atropine that does not have atropine's side effects. Ipratropium bromide may provide some additive benefit with inhaled beta₂-agonists in severe asthma exacerbations. Its effectiveness in long-term management of asthma has not been demonstrated (Kerstjens et al. 1992; Gross 1988; Storms et al. 1986).

Systemic Corticosteroids

Systemic corticosteroids can speed resolution of airflow obstruction and reduce the rate of relapse (Fanta et al. 1983; Rowe et al. 1992; Scarfone et al. 1993; Connett et al. 1994; Chapman et al. 1991).

Medications To Reduce Oral Systemic Corticosteroid Dependence

Troleandomycin, Cyclosporine, Methotrexate, Gold, Intravenous Immunoglobulin, Dapsone, and Hydroxychloroquine

These regimens to reduce oral systemic corticosteroid dependence should be used only in selected patients who are under the supervision of an asthma specialist. Although some of the compounds have corticosteroid-sparing effects, their use in asthma remains complicated because of highly variable effects, potential toxicity, and limited clinical experience (Bernstein et al. 1996; Jarjour et al. 1996; Mullarkey et al. 1988; Shiner et al. 1990; Erzurum et al. 1991; Muranaka et al. 1978; Klaustermeyer et al. 1987; Kamada et al. 1993; Nelson et al. 1993; Alexander et al. 1992; Mazer and Gelfand 1991). Colchicine is not considered effective in reducing need for oral systemic or high doses of inhaled corticosteroids (Newman et al. 1997).

Complementary Alternative Medicine

Alternative healing methods are not substitutes for recommended pharmacologic therapy. Although alternative healing methods may be popular with selected patients and of some interest to investigators, their scientific basis has not been established.

The most widely known complementary alternative medicine methods are acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine (which includes transcendental meditation, herbs, and yoga).

A review of multiple trials on the use of acupuncture in asthma concluded that the trials lacked quality and that the effectiveness of acupuncture in treating asthma has not been established (Kleijnen et al. 1991). One trial, however, demonstrated benefit in EIB (Fung et al. 1986). Homeopathy, based on the "law of similars" and the use of infinitesimally small doses, is as yet unproven for asthma (Reilly et al. 1986); some homeopathic remedies may contain potent unidentified pharmacologic agents (Morice 1986). No controlled clinical trials have been reported on herbal medicines, and the claims of effectiveness of western plant derivatives for asthma remain unsubstantiated (Dorsch and Wagner 1991; Ziment and Stein 1993). Because complementary alternative medicine is reported to be used by as much as one-third of the U.S. population (Eisenberg et al. 1993), it may be important to inquire about all the medications a patient uses and advise the patient accordingly (see component 4).

ROUTE OF ADMINISTRATION

Medications for asthma can be administered either by inhaled or systemic routes. Systemic routes are oral (ingested) or parenteral (subcutaneous, intramuscular, or intravenous). The major advantages of delivering drugs directly into the lungs via inhalation are that higher concentrations can be delivered more effectively to the airways and that systemic side effects are avoided or minimized (Newhouse and Dolovich 1986). Furthermore, the onset of action of inhaled bronchodilators is substantially shorter than that of oral bronchodilators.

Inhaled medications, or aerosols, are available in a variety of devices that differ in technique required and quantity of drug delivered to the lung. See figure 3-3 for a summary of issues to consider for different devices. Whatever device is selected, patients should be instructed in its use and their technique checked regularly.

Most inhaled medications currently used for asthma are available as metered-dose inhalers (MDIs). Historically, MDI technology has utilized chlorofluorocarbons (CFCs) as propellants. CFCs usually constitute 95 percent or more of the formulation emitted from an MDI; CFCs are metabolically stable and even the portion of an actuation that is systemically absorbed is quickly excreted unchanged via exhalation. However, CFCs have been found to deplete stratospheric ozone and have been banned internationally. Although a temporary medical exemption

has been granted, it is expected that CFC-propelled MDIs will eventually be phased out completely. Alternatives include MDIs with other propellants (nonchlorinated propellants such as hydrofluoroalkane [HFA] 134a do not have ozone-depleting properties), multidose dry powder inhalers, and other hand-held devices with convenience and delivery characteristics similar to current MDIs. An MDI for albuterol with HFA 134a has been approved for use; additional non-CFC products and delivery systems are expected in the future. The Food and Drug Administration approval process requires that the replacement products demonstrate comparability to the corresponding CFC products so that clinicians and patients can anticipate similar effectiveness and safety with the new products. During the phaseout of CFC products, clinicians will need to be informed of the alternatives and assist their patients in the transition to non-CFC products (see component 4).

SPECIAL ISSUES REGARDING SAFETY

Short-Acting Inhaled Beta₂-Agonists

KEY POINTS: SHORT-ACTING INHALED BETA₂-AGONISTS

- Short-acting beta₂-agonists are the most effective medication for relieving acute bronchospasm.
- Increasing use of short-acting beta₂-agonists or the use of more than one canister in 1 month indicates inadequate control of asthma and the need for initiating or intensifying anti-inflammatory therapy.
- Regularly scheduled, daily use of short-acting beta₂-agonists is generally not recommended.

Short-acting inhaled beta₂-agonists (e.g., albuterol) are the medications of choice for treating exacerbations of asthma and for preventing EIB. Prior to 1990, many clinicians prescribed short-acting beta₂-agonists on a regularly scheduled basis in the belief that this treatment regimen improved overall asthma symptom control. Some recent reports, however, have modified these beliefs. For example, in *moderate* asthma, regular use of a potent inhaled beta₂-agonist (fenoterol) produced a significant diminution in asthma control and objective measurements of pulmonary function (Sears et al. 1990). In *mild* asthma, regularly scheduled use of albuterol compared to use on an as-needed basis only resulted in no significant differences in a variety of

FIGURE 3-3. AEROSOL DELIVERY DEVICES

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
<p>Metered-dose inhaler (MDI)</p> <p>Beta₂-agonists</p> <p>Corticosteroids</p> <p>Cromolyn sodium and nedocromil</p> <p>Anticholinergics</p>	>5 years	<p>Actuation during a slow (30 L/min or 3-5 seconds) deep inhalation, followed by 10-second breath-holding.</p> <p>Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. However, it has not consistently been shown to enhance clinical benefit compared to closed-mouth technique (closing lips around MDI mouthpiece).</p>	<p>Slow inhalation may be difficult. Difficulty with coordination of actuation and inhalation, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 80 percent of actuated dose in oropharynx. Mouth washing is effective in reducing systemic absorption (Selroos and Halme 1991).</p>
<p>Breath-actuated MDI</p> <p>Beta₂-agonists</p>	>5 years	<p>Slow (30 L/min or 3-5 seconds) inhalation followed by 10-second breath-holding.</p>	<p>Indicated for patients unable to coordinate inhalation and actuation. May be particularly useful in elderly (Newman et al. 1991). Slow inhalation may be difficult and patients may incorrectly stop inhalation at actuation. Requires more rapid inspiration to activate than is optimal for deposition. Cannot be used with currently available spacer/holding chamber devices.</p>
<p>Dry powder inhaler (DPI)</p> <p>Beta₂-agonists</p> <p>Corticosteroids</p>		<p>Rapid (60 L/min or 1-2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent.</p>	<p>Dose lost if patient exhales through device. Delivery may be >MDI depending on device and technique. Can be used in children 4 years old, but effects are more consistent with children >5 (Pedersen et al. 1990; Goren et al. 1994; Kemp et al. 1989; Kesten et al. 1994). Most appear to have similar delivery efficiency as MDI either with or without spacer/holding chamber, but some may have delivery >MDI (Thorsson et al. 1994; Agertoft and Pedersen 1993; Kemp et al. 1989; Meichor et al. 1993; Vidgren et al. 1983). Mouth washing is effective in reducing systemic absorption (Selroos and Halme 1991).</p>

FIGURE 3-3. AEROSOL DELIVERY DEVICES (CONTINUED)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Spacer/holding chamber	>4 years ≤4 years with face mask	Slow (30 L/min or 3-5 seconds) inhalation or tidal breathing immediately following actuation. Actuation only once into spacer/holding chamber per inhalation (O'Callaghan et al. 1994). If face mask is used, allow 3-5 inhalations per actuation (Everard et al. 1992).	Easier to use than MDI alone. With a face mask, enables MDI to be used with small children (Everard et al. 1992; Connett et al. 1993). Simple tubes do not obviate coordinating actuation and inhalation. Bulky. Output may be reduced in some devices after cleaning. The larger volume spacers/holding chambers (>600 cc) may increase lung delivery over MDI alone in patients with poor MDI technique. The effect of a spacer/holding chamber on output from an MDI is dependent on both MDI and spacer type; thus data from one combination should not be extrapolated to all others (Ahrens et al. 1995; Kim et al. 1987). Spacers/holding chambers decrease oropharyngeal deposition and will reduce potential system absorption of inhaled corticosteroid preparations that have higher oral bioavailability (Newman et al. 1984; Brown et al. 1990; Lipworth 1995; Selroos and Halme 1991). Spacers/holding chambers are recommended for all patients on medium-to-high doses of inhaled corticosteroids. May be as effective as nebulizer in delivering high doses of beta ₂ -agonists during severe exacerbations.
Nebulizer Beta ₂ -agonists Cromolyn Anticholinergics Corticosteroids	<2 years Patients of any age who cannot use MDI with spacer/holding chamber or spacer and face mask (e.g., during exacerbations)	Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece.	Less dependent on patient coordination or cooperation. Delivery method of choice for cromolyn in children and for high-dose beta ₂ -agonists and anticholinergics in moderate-to-severe exacerbations in all patients. Expensive; time consuming; bulky; output is device dependent; and there are significant internebulizer and intranebulizer output variances.

* See figure 4-3 for description of MDI and DPI techniques.

Sources: Agertoft and Pedersen 1993; Ahrens et al. 1995; Brown et al. 1990; Connett et al. 1993; Higgins et al. 1987; Crompton and Duncan 1989; Everard et al. 1992; Fuglsang and Pedersen 1986; Goren et al. 1994; Kemp et al. 1989; Kesten et al. 1994; Kim et al. 1987; Lipworth 1995; Melchor et al. 1993; Newman et al. 1981, 1984, 1991; O'Callaghan et al. 1994; Pedersen et al. 1990; Pedersen and Mortensen 1990; Prahl and Jenson 1987; Rossing et al. 1980; Ruggins et al. 1993; Schecker et al. 1993; Selroos and Halme 1991; Selroos et al. 1995; Thorsson et al. 1994; Vidgren et al. 1983.

outcome indices. Although regularly scheduled use of beta₂-agonists in mild asthma produced no harmful effects in a 4-month period, it also produced no demonstrable benefits (Drazen et al. 1996). Similar findings were noted in studies with moderate asthma (D'Alonzo et al. 1994; Pearlman et al. 1992). Based on these and other observations (Cockcroft et al. 1993; van Schayck et al. 1991; O'Connor et al. 1992; Mullen et al. 1993; Ernst et al. 1993; Suissa et al. 1994), the regularly scheduled, daily use of short-acting beta₂-agonists is not generally recommended.

The frequency of beta₂-agonist use can be clinically useful as a barometer of disease activity because increasing use of beta₂-agonists has been associated with increased risk for death or near death in patients with asthma (Spitzer et al. 1992). The use of more than one beta₂-agonist canister (e.g., albuterol, 200 puffs per canister) predominantly for quick-relief treatment during a 1-month period most likely indicates overreliance on this drug and suggests inadequate asthma control (Spitzer et al. 1992).

Long-Acting Inhaled Beta₂-Agonists

KEY POINTS: LONG-ACTING INHALED BETA₂-AGONISTS

- Long-acting beta₂-agonists (salmeterol) can be beneficial to patients when added to inhaled corticosteroid therapy, especially to control nighttime symptoms (Greening et al. 1994; Woolcock et al. 1996). Daily use of long-acting beta₂-agonists should generally not exceed 84 mcg (salmeterol; four puffs).
- *Salmeterol is not to be used for treatment of acute symptoms or exacerbations.*
- Patient education regarding correct use of salmeterol is critical.
- Patients should be instructed not to stop anti-inflammatory therapy while taking salmeterol even though their symptoms may significantly improve.

Long-acting beta₂-agonists have several beneficial clinical properties. They attenuate EIB for longer time periods than do short-acting beta₂-agonists (Green and Price 1992; Henriksen et al. 1992) and improve nocturnal asthma symptoms (Fitzpatrick et al. 1990; Maesen et al. 1990). Recent studies suggest that for patients with inadequate symptom control who are receiving low-to-medium doses of inhaled

corticosteroids, it may be more beneficial to add salmeterol than to increase the dose of inhaled corticosteroids (Greening et al. 1994; Woolcock et al. 1996). Furthermore, in one study, salmeterol resulted in statistically significant increases in overall quality of life (Juniper et al. 1995) although the clinical significance of the reported differences is not certain.

Several studies report that patients do not appear to develop a tolerance to the bronchodilator action of salmeterol even after months of regular treatment (D'Alonzo et al. 1994; Lotvall et al. 1992; Pearlman et al. 1992; Uilman et al. 1990). In contrast, in bronchoprovocation studies following chronic administration of either short-acting or long-acting beta₂-agonists, a decrease was demonstrated in the bronchoprotective effect against exercise (Ramage et al. 1994), allergen (Cockcroft et al. 1993, 1995; Bhagat et al. 1996), and methacholine (Bhagat et al. 1996; Cheung et al. 1992). However, the bronchoprotective effect over time, although diminished, was still significantly greater than placebo. Thus, the clinical importance of the reported decrease in bronchoprotective effect remains uncertain (McFadden 1995).

Following the introduction of salmeterol into clinical practice, case reports of sudden severe attacks of asthma (Clark et al. 1993) raised concerns that in certain asthma patients, under certain conditions, the use of salmeterol may cause a sudden worsening of symptoms and possibly death. A recent randomized study in England compared more than 16,000 patients who received regular salmeterol for a 16-week period with more than 8,000 patients receiving regular (qid) albuterol therapy. The study found more deaths in the salmeterol group; however, the differences did not reach statistical significance (Castle et al. 1993). Nor did a prescription-event monitoring survey demonstrate a statistically significant difference in deaths (Mann et al. 1996). Several large studies have demonstrated that, overall, patients taking salmeterol do not experience an increase in the frequency of exacerbations (Britton et al. 1992; Lundback et al. 1993; Greening et al. 1994; Pearlman et al. 1992; Woolcock et al. 1996). There are ongoing longitudinal studies to determine if there might be risk for special populations. The potential for patients to incorrectly use salmeterol as a quick-relief medication warrants special attention by the clinician and appropriate patient education. Based on current information, long-acting inhaled beta₂-agonists should be used only in conjunction with anti-inflammatory medication. When added to inhaled corticosteroids, long-acting inhaled beta₂-agonists are helpful long-term-control therapy.

Inhaled Corticosteroids

KEY POINTS: INHALED CORTICOSTEROIDS

- Inhaled corticosteroids are the most effective long-term therapy available for mild, moderate, or severe persistent asthma; in general, inhaled corticosteroids are well tolerated and safe at the recommended dosages.
- The potential but small risk of adverse events from the use of inhaled corticosteroids is well balanced by their efficacy.
- To reduce the potential for adverse effects, the following measures are recommended:
 - Administer inhaled corticosteroids with spacers/holding chambers.
 - Advise patients to rinse their mouths (rinse and spit) following inhalation.
 - Use the lowest possible dose of inhaled corticosteroid to maintain control.
 - To maintain control of asthma (especially for nocturnal symptoms), consider adding a long-acting inhaled beta₂-agonist to a low-to-medium dose of inhaled corticosteroid rather than using a higher dose of inhaled corticosteroid.
 - For children, monitor growth (see box on page 72).
 - For postmenopausal women, consider supplements of calcium (1,000 to 1,500 mg per day) and vitamin D (400 units a day). Estrogen replacement therapy, where appropriate, may be considered for patients on doses that exceed 1,000 mcg of inhaled corticosteroid a day.

Inhaled corticosteroids are the most effective long-term therapy available for patients with persistent asthma. In general, inhaled corticosteroids are well tolerated and safe at the recommended dosages (Barnes 1995; van Essen-Zandvliet et al. 1992; Tinkelman et al. 1993). Systemic effects have been identified, particularly at high doses (see figure 3-5b for a definition of high-, medium-, and low-dose inhaled corticosteroids), but their clinical significance remains unclear. Furthermore, there may be interindividual variations in dose-response effects, and thus some patients may experience effects at lower doses. (See Key Points above for a summary of recommendations to minimize the potential for adverse effects.) In general, the potential for adverse

effects must be weighed against the risk of uncontrolled asthma; to date evidence supports the use of inhaled corticosteroids, especially at low and medium doses.

Local Adverse Effects

Oral candidiasis (thrush) is one of the most common adverse effects of inhaled corticosteroids. Positive throat cultures of *Candida* can be identified in about 45 to 58 percent of patients, whereas clinical thrush is diagnosed in only 0 to 34 percent of patients (Rinehart et al. 1975; Toogood et al. 1980; Shaw and Edmunds 1986). With lower dosages of inhaled corticosteroids, candidiasis is uncommon (5 percent) (Rinehart et al. 1975), although it is more frequent in adults than in children. **Prevention and treatment:** Use a spacer/holding chamber to reduce the incidence of colonization and clinical thrush, rinse mouth with water after inhalation (Selroos and Halme 1991), and administer inhaled corticosteroids less frequently (bid vs. qid). Topical or oral antifungal agents should be used to treat active infections.

Dysphonia is reported in 5 to 50 percent of patients using inhaled corticosteroids and is associated with vocal stress and increasing dosages of inhaled corticosteroids (Toogood et al. 1980). **Prevention and treatment:** Use a spacer/holding chamber, temporarily reduce dosage, or rest for vocal stress.

Reflex cough and bronchospasm can be reduced by slower rates of inspiration and/or use of a spacer/holding chamber or pretreatment with an inhaled beta₂-agonist. There is no convincing evidence that the routine use of an inhaled beta₂-agonist prior to each dose of inhaled corticosteroids increases intrapulmonary delivery of the inhaled corticosteroid or reduces dosage requirement.

Systemic Adverse Effects

Linear Growth. The potential effects of inhaled corticosteroids on children's growth are important because the drugs are more likely to be used for longer periods of time, although it is recognized that poorly controlled asthma itself may result in retarded linear growth. Growth in children with asthma who have not received any form of corticosteroid therapy may be influenced by concomitant atopy, asthma severity, and being male, among other factors (Kamada and Szefer 1995; Allen 1996). Indeed, childhood asthma appears to be associated with

KEY POINTS: INHALED CORTICOSTEROIDS AND LINEAR GROWTH IN CHILDREN

- The potential risks of inhaled corticosteroids are well balanced by their benefits.
- Growth rates are highly variable in children. Short-term evaluations may not be predictive of attaining final adult height.
- Poorly controlled asthma may delay growth in children.
- In general, children with asthma tend to have longer periods of reduced growth rates prior to puberty (males > females).
- The potential for adverse effects on linear growth from inhaled corticosteroids appears to be dose dependent. In treating children with *mild-to-moderate persistent asthma*, medium-dose inhaled corticosteroid therapy may be associated with a possible, but not predictable, adverse effect on linear growth. The clinical significance of this potential systemic effect has yet to be determined. High doses of inhaled corticosteroids have greater potential for growth suppression.
- Use of high doses of inhaled corticosteroids with children with *severe persistent asthma* has significantly less potential for having an adverse effect on linear growth than oral systemic corticosteroids.
- A majority of studies of the use of inhaled corticosteroids by children have not demonstrated an effect on growth, but a few have identified growth delay. Some caution (e.g., monitoring growth, stepping down therapy when possible) is suggested while this issue is studied further.

delayed maturation and a longer period of reduced growth prior to puberty. Although this could be viewed as growth suppression, these delays do not appear to compromise the attainment of final predicted adult heights (Balfour-Lynn 1986; Allen 1996).

Because of these numerous confounding factors, evaluating the effects of systemic or inhaled corticosteroids on growth in children with asthma has been challenging and has led to contradictory findings.

A few studies of children with asthma have identified some growth delay in those treated with inhaled corticosteroids, suggesting that some caution may be

prudent until this important issue can be studied further. A 1-year controlled trial comparing children with mild-to-moderate asthma receiving either inhaled beclomethasone (400 mcg per day, administered without a spacer/holding chamber) or oral theophylline demonstrated slower growth in children receiving beclomethasone (Tinkelman et al. 1993). In a placebo-controlled, community-based 7-month study of 7- to 9-year-old children to determine the effect on growth during treatment with beclomethasone at 400 mcg/day, growth was significantly decreased in both males and females, and there was no evidence of catchup growth during a 5-month washout period (Doull et al. 1995). However, the results of this short-term study may not reflect effects on long-term growth.

A recent meta-analysis of the influence of inhaled beclomethasone in the attainment of expected adult height did not find any significant adverse effects regardless of dose, duration of asthma, or disease severity (Allen et al. 1994). An uncontrolled followup study (mean duration of 2.7 years, range of 1 to 5 years) of prepubertal children with moderate asthma found no effect of inhaled budesonide (800 mcg mean daily dose) on long-term growth (Ninan and Russell 1992). A majority of studies do not demonstrate a negative effect on growth with dosages of 400 to 800 mcg a day (Woithers 1996; Kamada et al. 1996; Kamada and Szefer 1995; Barnes and Pederson 1993).

Bone Metabolism/Osteoporosis. The few published observations regarding the effect of inhaled corticosteroids on bone metabolism and osteoporosis are complicated by oral corticosteroid use and small patient populations (Jennings et al. 1991a, 1991b; Toogood et al. 1991). The effects of inhaled corticosteroid on markers of skeletal metabolism—serum osteocalcin, serum alkaline phosphatase, and urinary hydroxyproline:creatinine ratio—are equivocal (Hodsman et al. 1991; Jennings et al. 1991a; Ali et al. 1991). The clinical implications in terms of risk of osteoporosis and fracture after long-term use of inhaled corticosteroids are still unknown (Jennings et al. 1991b; Pouw et al. 1991). Although low and medium dosages of inhaled corticosteroids appear to have no major adverse effects on any clinically important measure of bone metabolism (Toogood et al. 1991, 1995), a dose-dependent, yet significant, reduction in bone mineral content of subjects with asthma has been associated with inhaled corticosteroid use (Packe et al. 1992; Puolijoki et al. 1992; Toogood

et al. 1988). Elderly female patients may be more at risk due to preexisting osteoporosis, previous use of oral corticosteroids, a sedentary lifestyle, and the normal changes of estrogen in aging that affect calcium utilization. However, the risk of uncontrolled asthma, which may unnecessarily limit the patient's mobility and activities, must be weighed against the limited risks of using inhaled corticosteroids. **Prevention and treatment:** Concurrent treatment with calcium supplements and vitamin D (and estrogen replacement where appropriate) is reasonable.

Disseminated Varicella. Although high doses of inhaled corticosteroids theoretically present risks similar to those of systemic corticosteroids, the reports of disseminated varicella in patients receiving only inhaled corticosteroids are rare, causality is not clear, and there is no evidence that recommended doses of inhaled corticosteroids are immunosuppressive. Cases have been reported of children with severe persistent asthma on immunosuppressive doses of systemic corticosteroids developing fatal disseminated disease from varicella infection (Kasper and Howe 1990; Silk et al. 1988). Other case reports indicate complications for patients with *Strongyloides* or tuberculosis who take high doses of systemic corticosteroids.

Prevention and treatment: Children who require episodic therapy with systemic corticosteroids who have not had clinical varicella should receive the varicella vaccine. The vaccine should not be administered to patients who are receiving immunosuppressive doses of systemic corticosteroids (2 mg/kg or more of prednisone equivalent or 20 mg/day of prednisone for more than 1 month), unless this dosage is discontinued for at least 1 month. Children who have completed a short prednisone course may receive varicella vaccine without delay (American Academy of Pediatrics 1995; CDC 1994). Children and adults on treatment with immunosuppressive doses of corticosteroids who have not been immunized against varicella and are exposed to varicella infection are candidates for zoster immunoglobulin and therapy with oral acyclovir. Should they develop clinical varicella, intravenous acyclovir with or without zoster immunoglobulin should be given.

Dermal thinning and increased ease of skin bruising have been observed in elderly subjects treated with inhaled corticosteroids. The effect is dose dependent, but the threshold dose is variable (Capewell et al. 1990).

Hypothalamic Pituitary Axis (HPA) Function.

The issue of inhaled corticosteroid effects on HPA function is complex and requires further study. Several studies indicate that low-to-medium doses of inhaled corticosteroids do not appear to have significant effects on HPA function (Doull et al. 1995; Goldstein and Konig 1983). However, some studies showed that, compared with placebo, both beclomethasone and budesonide reduced the 24-hour urinary cortisol excretion even in doses as low as 400 to 500 mcg daily (Tabachnik and Zadik 1991; Prah 1991). At higher doses, there appears to be a dose-dependent effect on different measures of HPA function (Kamada et al. 1996; Brown et al. 1993). Fluticasone caused greater adrenal suppression at doses of 400 to 2,000 mcg than budesonide in equivalent doses (Clark et al. 1996; Boorsma et al. 1996). The clinical significance, if any, of these findings is not known.

Cataracts. Although cataracts are a documented adverse effect of systemic corticosteroids, there appears to be no association between inhaled corticosteroids and posterior subcapsular cataracts in adults (Toogood et al. 1993) or children (Simons et al. 1993; Rooklin et al. 1979).

Glucose Metabolism. In a study of children, inhaled corticosteroids at dosages from 400 to 1,000 mcg/day (budesonide) failed to affect fasting glucose or glycosylated hemoglobin (Turpeinen et al. 1991). At 1,000 mcg/day, a significantly greater rise in fasting serum insulin levels and glucose during a glucose tolerance test was noted, but results remained within normal limits.

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Pharmacologic Therapy: Managing Asthma Long Term

KEY RECOMMENDATIONS FOR MANAGING ASTHMA LONG TERM

- Persistent asthma is most effectively controlled with daily long-term-control medication, specifically, anti-inflammatory therapy.
- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma:
 - The amount and frequency of medication is dictated by asthma severity and directed toward suppression of airway inflammation.
 - Therapy should be initiated at a higher level than the patient's step of severity at the onset to establish prompt control and then stepped down.
 - Continual monitoring is essential to ensure that asthma control is achieved.
 - Step-down therapy is essential to identify the minimum medication necessary to maintain control.
- Regular followup visits (at 1- to 6-month intervals) are essential to ensure that control is maintained and the appropriate step down in therapy is considered.
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy.
- At each step, patients should be advised to avoid or control allergens, irritants, or other factors that make the patient's asthma worse.
- Referral to an asthma specialist for consultation or comanagement of the patient is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care (see component 1-Initial Assessment and Diagnosis). Referral may be considered if the patient requires step 3 care. For infants and young children, referral is recommended if the patient requires step 3 or 4 care and should be considered if the patient requires step 2 care.

STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE

The aim of asthma therapy is to maintain control of asthma with the least amount of medication and hence minimal risk for adverse effects. Control of asthma is defined as:

- Preventing chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintaining (near) "normal" pulmonary function
- Maintaining normal activity levels (including exercise and other physical activity)
- Preventing recurrent exacerbations of asthma and minimizing the need for emergency department visits or hospitalizations
- Providing optimal pharmacotherapy with minimal or no adverse effects
- Meeting patients' and families' expectations of and satisfaction with asthma care

The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve this control. This is illustrated in figures 3-4a and 3-4b. Figures 3-5a and 3-5d present usual medication dosages for therapy. Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, therapy for persistent asthma must emphasize efforts to suppress inflammation over the long term and prevent exacerbations. Recommendations in the stepwise approach to therapy are based on the Expert Panel's review of the literature (see component 3-Medications) and the Expert Panel's experience and opinion.

Gaining Control of Asthma

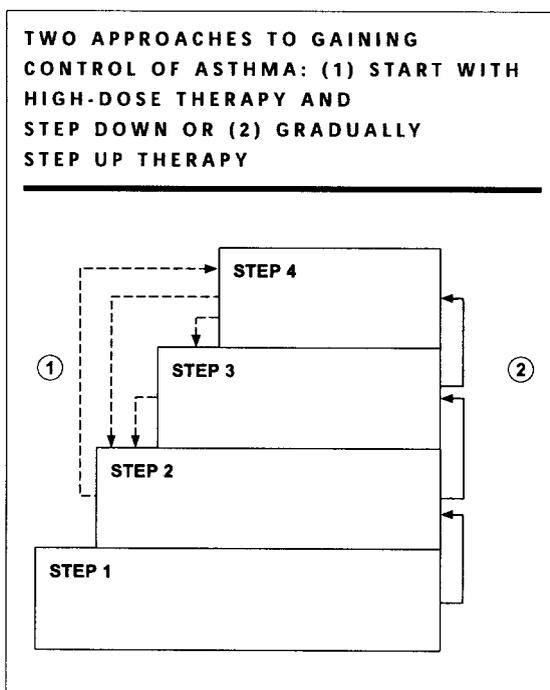
The clinician must judge individual patient needs and circumstances to determine at what step to initiate therapy. There are two appropriate approaches to gaining control of asthma:

- Start treatment at the step appropriate to the severity of the patient's disease at the time of evaluation and gradually step up if control is not achieved.

OR

- At the onset, administer therapy at a level higher than the patient's step of severity to gain rapid control. This can be accomplished by either a short course of systemic corticosteroids (see figure 3-5a) along with inhaled corticosteroids or initiating a medium-to-high dose of inhaled corticosteroids. Once control is gained, step down the therapy.

The two approaches are illustrated by the solid and broken lines in the following diagram.



The more aggressive approach of gaining prompt control with a higher level of therapy is preferred, in the opinion of the Expert Panel. At present, there are no studies directly comparing the

two approaches—the traditional step-up care (low dose to high) vs. step-down care (initial high dose to low). However, there is evidence supporting a more aggressive initial approach. First, asthma symptoms and altered pulmonary function are related to the level of ongoing airway inflammation. Suppression of airway inflammation is more likely to occur with higher doses of corticosteroids. Furthermore, studies indicate that the dose of inhaled or systemic corticosteroids can be reduced and the clinical benefits sustained once the disease is controlled (Haahtela et al. 1994; Agertoft and Pedersen 1994). A preliminary observation in a retrospective study of children suggests that initiating inhaled corticosteroids early in the course of the disease results in better clinical benefit and less accumulated corticosteroid dose over the long term (Agertoft and Pedersen 1994). Therefore, it is conceivable that a more aggressive approach in initial therapy will more rapidly suppress airway inflammation, restore pulmonary function, and allow for eventual asthma control at lower doses of anti-inflammatory therapy.

Continual monitoring is essential to ensure that asthma control is achieved. Control is indicated by, for example, peak expiratory flow (PEF) values indicating less than 10 to 20 percent variability or PEF consistently greater than 80 percent of the patient's personal best, minimal symptoms, minimal need for short-acting inhaled beta₂-agonist, absence of nighttime awakenings, and no activity limitations.

If control is not achieved with initial therapy (e.g., within 1 month), the pharmacologic management plan, and possibly the diagnosis, should be reevaluated (see Pharmacologic Steps, page 87).

Maintaining Control of Asthma

Once control is achieved and sustained for several weeks or months, a reduction in pharmacologic therapy—a step down—is appropriate and helpful to identify the minimum therapy for maintaining control. Reduction in therapy should be gradual because asthma can deteriorate at a highly variable rate and intensity.

In general, the last medication added to the medical regimen should be the first medication reduced. Although guidelines for the rate of reduction and intervals for evaluation have not been established, the opinion of the Expert Panel is that the dose of inhaled corticosteroids may be reduced about

FIGURE 3-4a. STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE

Goals of Asthma Treatment

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

Classify Severity of Asthma			
Clinical Features Before Treatment*			
	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	<ul style="list-style-type: none"> ■ Continual symptoms ■ Limited physical activity ■ Frequent exacerbations 	Frequent	<ul style="list-style-type: none"> ■ FEV₁ or PEF ≤ 60% predicted ■ PEF variability >30%
STEP 3 Moderate Persistent	<ul style="list-style-type: none"> ■ Daily symptoms ■ Daily use of inhaled short-acting beta₂-agonist ■ Exacerbations affect activity ■ Exacerbations ≥2 times a week; may last days 	>1 time a week	<ul style="list-style-type: none"> ■ FEV₁ or PEF >60% – <80% predicted ■ PEF variability >30%
STEP 2 Mild Persistent	<ul style="list-style-type: none"> ■ Symptoms >2 times a week but <1 time a day ■ Exacerbations may affect activity 	>2 times a month	<ul style="list-style-type: none"> ■ FEV₁ or PEF ≥ 80% predicted ■ PEF variability 20–30%
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> ■ Symptoms ≤2 times a week ■ Asymptomatic and normal PEF between exacerbations ■ Exacerbations brief (from a few hours to a few days); intensity may vary 	≤2 times a month	<ul style="list-style-type: none"> ■ FEV₁ or PEF ≥80% predicted ■ PEF variability <20%

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

** Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

FIGURE 3-4b. STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE: TREATMENT

Preferred treatments are in bold print

	Long-Term Control	Quick Relief	Education
STEP 4 Severe Persistent	<p>Daily medications:</p> <ul style="list-style-type: none"> ■ Anti-inflammatory: inhaled corticosteroid (high dose) <p>AND</p> <ul style="list-style-type: none"> ■ Long-acting bronchodilator: either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets <p>AND</p> <ul style="list-style-type: none"> ■ Corticosteroid tablets or syrup long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids) 	<ul style="list-style-type: none"> ■ Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. ■ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ■ Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy. 	<p>Steps 2 and 3 actions plus:</p> <ul style="list-style-type: none"> ■ Refer to individual education/counseling
STEP 3 Moderate Persistent	<p>Daily medication:</p> <ul style="list-style-type: none"> ■ Either Anti-inflammatory: inhaled corticosteroid (medium dose) <p>OR</p> <p>Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets.</p> <ul style="list-style-type: none"> ■ If needed Anti-inflammatory: inhaled corticosteroids (medium-high dose) <p>AND</p> <p>Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets.</p>	<ul style="list-style-type: none"> ■ Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. ■ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ■ Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy. 	<p>Step 1 actions plus:</p> <ul style="list-style-type: none"> ■ Teach self-monitoring ■ Refer to group education if available ■ Review and update self-management plan

FIGURE 3-4b. STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE: TREATMENT (CONTINUED)

Preferred treatments are in bold print.

	Long-Term Control	Quick Relief	Education
STEP 2 Mild Persistent	One daily medication: ■ Anti-inflammatory: either inhaled corticosteroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil). ■ Sustained-release theophylline to serum concentration of 5-15 mcg/mL is an alternative, but not preferred, therapy. Zafirlukast or zileuton may also be considered for patients >12 years of age, although their position in therapy is not fully established.	■ Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. ■ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ■ Use of short-acting inhaled beta ₂ -agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.	Step 1 actions plus: ■ Teach self-monitoring ■ Refer to group education if available ■ Review and update self-management plan
STEP 1 Mild Intermittent	■ No daily medication needed.	■ Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. ■ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ■ Use of short-acting inhaled beta ₂ -agonists more than 2 times a week may indicate the need to initiate long-term-control therapy.	■ Teach basic facts about asthma ■ Teach inhaler/spacer/holding chamber technique ■ Discuss roles of medications ■ Develop self-management plan ■ Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations ■ Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants (See component 4.)
Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.		Step up If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control (avoidance of allergens or other factors that contribute to asthma severity).	

NOTE:

- The stepwise approach presents general guidelines to assist clinical decisionmaking; it is not intended to be a specific prescription. Asthma is highly variable; clinicians should tailor specific medication plans to the needs and circumstances of individual patients.
- Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition or starting at a higher level of therapy (e.g., a course of systemic corticosteroids or higher dose of inhaled corticosteroids).
- A rescue course of systemic corticosteroids may be needed at any time and at any step.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may be especially common with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- At each step, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diagnosis and education.
- Referral to an asthma specialist for consultation or comanagement is *recommended* if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be *considered* if the patient requires step 3 care (see also component 1-Initial Assessment and Diagnosis).

FIGURE 3-5a. USUAL DOSAGES FOR LONG-TERM-CONTROL MEDICATIONS

Medication	Dosage Form	Adult Dose	Child Dose	Comments
<i>Inhaled Corticosteroids</i> (see figures 3-5b and 3-5c)				
<i>Systemic Corticosteroids</i>			(Applies to all three systemic corticosteroids)	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	■ 7.5–60 mg daily in a single dose or qod as needed for control	■ 0.25–2 mg/kg daily in single dose or qod as needed for control	<ul style="list-style-type: none"> ■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). If daily doses are required, one study suggests improved efficacy and no increase in adrenal suppression when administered at 3:00 p.m. (Beam et al. 1992). ■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	■ Short-course "burst": 40–60 mg per day as single or 2 divided doses for 3–10 days	■ Short course "burst": 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	
Prednisone	1, 2.5, 5, 10, 20, 25 mg tablets; 5 mg/cc, 5 mg/5 cc			
<i>Cromolyn and Nedocromil</i>				
Cromolyn	MDI 1 mg/puff Nebulizer solution 20 mg/ampule	2–4 puffs tid-qid 1 ampule tid-qid	1–2 puffs tid-qid 1 ampule tid-qid	<ul style="list-style-type: none"> ■ One dose prior to exercise or allergen exposure provides effective prophylaxis for 1–2 hours.
Nedocromil	MDI 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid	<ul style="list-style-type: none"> ■ See cromolyn above.
<i>Long-Acting Beta₂-Agonists</i>				
Salmeterol	<i>Inhaled</i> MDI 21 mcg/puff, 60 or 120 puffs DPI 50 mcg/blister	2 puffs q 12 hours 1 blister q 12 hours	1–2 puffs q 12 hours 1 blister q 12 hours	<ul style="list-style-type: none"> ■ May use one dose nightly for symptoms. ■ Should not be used for symptom relief or for exacerbations.
Sustained-Release Albuterol	<i>Tablet</i> 4 mg tablet	4 mg q 12 hours	0.3–0.6 mg/kg/day, not to exceed 8 mg/day	
<i>Methylxanthines</i>				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: <ul style="list-style-type: none"> ■ < 1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥ 1 year of age: 16 mg/kg/day 	<ul style="list-style-type: none"> ■ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ■ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important. ■ See factors on page 87 that can affect levels.
<i>Leukotriene Modifiers</i>				
Zafirlukast	20 mg tablet	40 mg daily (1 tablet bid)		<ul style="list-style-type: none"> ■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ For zileuton, monitor hepatic enzymes (ALT).
Zileuton	300 mg tablet 600 mg tablet	2,400 mg daily (two 300 mg tablets or one 600 mg tablet, qid)		

FIGURE 3-5a. USUAL DOSAGES FOR LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Factors Affecting Serum Theophylline Concentrations*			
Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods) products	Select theophylline preparation that is not affected by food.
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration level. Decrease dose by 50 percent if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration level.
Age	↑ metabolism (1 to 9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration level.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration level.
Cimetidine		↓ metabolism	Use alternative H ₂ blocker (e.g., famotidine or ranitidine).
Macrolides: TAO, erythromycin, clarithromycin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, pefloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose. Circumvent with ofloxacin if quinolone therapy is required.
Rifampin	↑ metabolism		Increase dose according to serum concentration level.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration level.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration level.

* This list is not all-inclusive; for discussion of other factors, see package inserts.

25 percent every 2 to 3 months to the lowest dose possible required to maintain control. It is likely that most patients with persistent asthma will continue to benefit from daily medication to suppress underlying airway inflammation. Patients may relapse when inhaled corticosteroids are completely discontinued (Vaalkens et al. 1993).

Regular followup visits (at 1- to 6-month intervals) are essential. Clinicians need to assess whether control of asthma has been maintained and if a step down in therapy is appropriate. Clinicians also need to monitor and review the daily self-management and action plans, the medications, and the patient's self-management behaviors (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate their asthma) (see figure 4-2).

The Expert Panel *recommends* referral to an asthma specialist for consultation or comanagement of the patient if: there are difficulties achieving or maintaining control of asthma; immunotherapy is being considered; the patient requires step 4 care (step 3 or 4 care for infants and young children); or the patient has had a life-threatening exacerbation (see component 1-Initial Assessment and Diagnosis). Referral may be *considered* if a patient requires step 3 care (or step 2 care for infants and young children).

Pharmacologic Steps

The following recommendations for pharmacologic therapy at different steps of asthma severity (see figures 3-4a and 3-4b) are intended to be general guidelines for making therapeutic decisions. They are not

FIGURE 3-5b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS

Adults			
Drug	Low Dose	Medium Dose	High Dose
Beclomethasone dipropionate 42 mcg/puff 84 mcg/puff	168-504 mcg (4-12 puffs — 42 mcg) (2-6 puffs — 84 mcg)	504-840 mcg (12-20 puffs — 42 mcg) (6-10 puffs — 84 mcg)	>840 mcg (>20 puffs — 42 mcg) (>10 puffs — 84 mcg)
Budesonide DPI: 200 mcg/dose	200-400 mcg (1-2 inhalations)	400-600 mcg (2-3 inhalations)	>600 mcg (>3 inhalations)
Flunisolide 250 mcg/puff	500-1,000 mcg (2-4 puffs)	1,000-2,000 mcg (4-8 puffs)	>2,000 mcg (>8 puffs)
Fluticasone MDI: 44, 110, 220 mcg/puff DPI: 50, 100, 250 mcg/dose	88-264 mcg (2-6 puffs — 44 mcg) OR (2 puffs — 110 mcg) (2-6 inhalations — 50 mcg)	264-660 mcg (2-6 puffs — 110 mcg) (3-6 inhalations — 100 mcg)	>660 mcg (>6 puffs — 110 mcg) OR (>3 puffs — 220 mcg) (>6 inhalations — 100 mcg) OR (>2 inhalations — 250 mcg)
Triamcinolone acetonide 100 mcg/puff	400-1,000 mcg (4-10 puffs)	1,000-2,000 mcg (10-20 puffs)	>2,000 mcg (>20 puffs)
Children			
Drug	Low Dose	Medium Dose	High Dose
Beclomethasone dipropionate 42 mcg/puff 84 mcg/puff	84-336 mcg (2-8 puffs — 42 mcg) (1-4 puffs — 84 mcg)	336-672 mcg (8-16 puffs — 42 mcg) (4-8 puffs — 84 mcg)	>672 mcg (>16 puffs — 42 mcg) (>8 puffs — 84 mcg)
Budesonide DPI: 200 mcg/dose	100-200 mcg	200-400 mcg (1-2 inhalations — 200 mcg)	>400 mcg (>2 inhalations — 200 mcg)
Flunisolide 250 mcg/puff	500-750 mcg (2-3 puffs)	1,000-1,250 mcg (4-5 puffs)	>1,250 mcg (>5 puffs)
Fluticasone MDI: 44, 110, 220 mcg/puff DPI: 50, 100, 250 mcg/dose	88-176 mcg (2-4 puffs — 44 mcg) (2-4 inhalations — 50 mcg)	176-440 mcg (4-10 puffs — 44 mcg) OR (2-4 puffs — 110 mcg) (2-4 inhalations — 100 mcg)	>440 mcg (>4 puffs — 110 mcg) OR (>2 puffs — 220 mcg) (>4 inhalations — 100 mcg) OR (>2 inhalations — 250 mcg)
Triamcinolone acetonide 100 mcg/puff	400-800 mcg (4-8 puffs)	800-1,200 mcg (8-12 puffs)	>1,200 mcg (>12 puffs)

Note:

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- See figure 3-5c for an explanation of the rationale used for the comparative dosages. The reference point for the range in the dosages for children is data on the safety of inhaled corticosteroids in children, which, in general, suggest that the dose ranges are equivalent to beclomethasone dipropionate 200-400 mcg/day (low dose), 400-800 mcg/day (medium dose), and >800 mcg/day (high dose).
- Some dosages may be outside package labeling.
- Metered-dose inhaler (MDI) dosages are expressed as the actuator dose (the amount of drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, all of which is not available to the patient), which is used in many European countries and in some of the scientific literature. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation.

FIGURE 3-5c. ESTIMATED CLINICAL COMPARABILITY OF DOSES FOR INHALED CORTICOSTEROIDS

Data from in vitro and clinical trials suggest that the different inhaled corticosteroid preparations are not equivalent on a per puff or microgram basis. However, it is not entirely clear what implications these differences have for dosing recommendations in clinical practice because there are few data directly comparing the preparations. Relative dosing for clinical comparability is affected by differences in topical potency, clinical effects at different doses, delivery device, and bioavailability. *The Expert Panel developed recommended dose ranges (see figure 3-5b) for different preparations based on available data and the following assumptions and cautions about estimating relative doses needed to achieve comparable clinical effect.*

■ Relative topical potency using human skin blanching

- The standard test for determining relative topical anti-inflammatory potency is the topical vasoconstriction (MacKenzie skin blanching) test.
- The MacKenzie topical skin blanching test correlates with binding affinities and binding half-lives for human lung corticosteroid receptors (see table below) (Dahlberg et al. 1984; Högger and Rohdewald 1994).
- The relationship between relative topical anti-inflammatory effect and clinical comparability in asthma management is not certain. However, recent clinical trials suggest that different in vitro measures of anti-inflammatory effect correlate with clinical efficacy (Barnes and Pedersen 1993; Johnson 1996; Kamada et al. 1996; Ebden et al. 1986; Leblanc et al. 1994; Gustafsson et al. 1993; Lundback et al. 1993; Barnes et al. 1993; Fabbri et al. 1993; Langdon and Capsey 1994; Ayres et al. 1995; Rafferty et al. 1985; Bjorkander et al. 1982; Stiksa et al. 1982; Willey et al. 1982).

Medication	Topical Potency (Skin Blanching)*	Corticosteroid Receptor Binding Half-Life	Receptor Binding Affinity
Beclomethasone dipropionate (BDP)	600	7.5 hours	13.5
Budesonide (BUD)	980	5.1 hours	9.4
Flunisolide (FLU)	330	3.5 hours	1.8
Fluticasone propionate (FP)	1,200	10.5 hours	18.0
Triamcinolone acetonide (TAA)	330	3.9 hours	3.6

* Numbers are assigned in reference to dexamethasone, which has a value of "1" in the MacKenzie test.

■ Relative doses to achieve similar clinical effects

- Clinical effects are evaluated by a number of outcome parameters (e.g., changes in spirometry, peak flow rates, symptom scores, quick-relief beta₂-agonist use, frequency of exacerbations, airway responsiveness).
- The daily dose and duration of treatment may affect these outcome parameters differently (e.g., symptoms and peak flow may improve at lower doses and over a shorter treatment time than bronchial reactivity) (van Essen-Zandvliet et al. 1992; Haahtela et al. 1991).
- Delivery systems influence comparability. For example, the DPI delivery device for budesonide delivers approximately twice the amount of drug to the airway as the MDI, thus enhancing the clinical effect (Thorsson et al. 1994; Agertoft and Pedersen 1993).
- *Individual patients may respond differently to different preparations, as noted by clinical experience.*

Clinical trials comparing effects in reducing symptoms and improving peak expiratory flow demonstrate:

- BDP and BUD achieved comparable effects at similar microgram doses by MDI (Bjorkander et al. 1982; Ebden et al. 1986; Rafferty et al. 1985).
- BDP achieved effects similar to twice the dose of TAA on a microgram basis.
- FP achieved effects similar to twice the dose of BDP and BUD via an MDI on a microgram basis (Gustafsson et al. 1993; Fabbri et al. 1993; Barnes et al. 1993; Dahl et al. 1993; Ayres et al. 1995).
- BUD by dry powder inhaler achieved effects similar to twice the dose delivered by MDI, thus implying greater bronchial delivery by the delivery device (Thorsson et al. 1994; Agertoft and Pedersen 1993).

FIGURE 3-5c. ESTIMATED CLINICAL COMPARABILITY OF DOSES FOR INHALED CORTICOSTEROIDS (CONTINUED)

■ **Bioavailability**

Both the relative potency and the relative bioavailability (systemic availability) determine the potential for systemic activity of an inhaled corticosteroid preparation. As illustrated here, the bioavailability of an inhaled corticosteroid is dependent on the absorption of the dose delivered to the lungs and the oral bioavailability of the swallowed portion of the dose received.

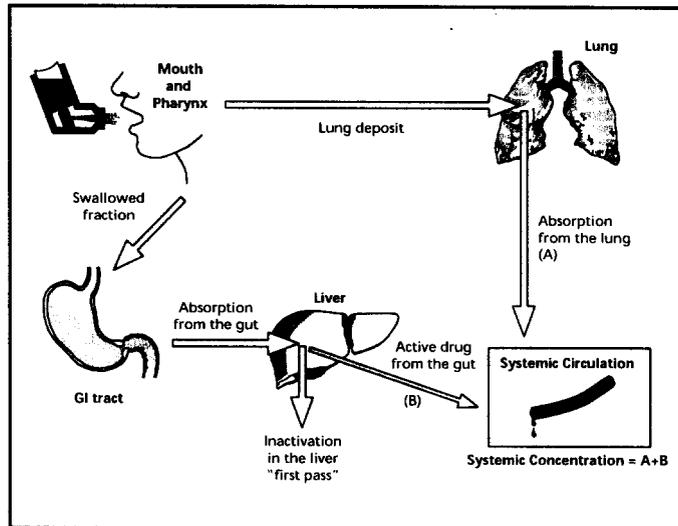
- Absorption of the dose delivered to the lungs:
 - Approximately 10 to 30 percent of the dose from the MDI is delivered to the lungs. This amount varies among preparations and delivery devices.
 - Nearly all of the amount delivered to the lungs is bioavailable.
- Oral bioavailability of the swallowed portion of the dose received:

- Approximately 80 percent of the dose from the MDI without a spacer/holding chamber is swallowed.
- The oral bioavailability of this amount varies:
 - Either a high first-pass liver metabolism or the use of a spacer/holding chamber with an MDI can decrease oral bioavailability, thus enhancing safety (Lipworth 1995).

The approximate oral bioavailability of inhaled corticosteroids has been reported as: BDP 20%; FLU 21%; TAA 10.6%; BUD 11%; FP 1% (Chaplin et al. 1980; Check and Kaliner 1990; Clissold and Heel 1984; Davies 1993; Harding 1990; Heald et al. 1995; Martin et al. 1974; Mollman et al. 1985; Szefer 1991; Wurthwein and Rohdewald 1990).

Although few clinical trials are available that compare systemic activity among preparations (Kamada et al. 1996), studies have found:

- As suggested by one cross-over comparison study, BDP, FLU, and TAA appear to have equivalent dose-dependent systemic activity, as measured by 24-hour urinary free cortisol excretion (McCubbin et al. 1995).
- Inconsistent results comparing BDP and BUD. Some show equivalent systemic activity (Kamada et al. 1996; Prah 1991; Prah et al. 1987); others show BUD having slightly less systemic activity than BDP (Barnes and Pedersen 1993; Pedersen and Fuglsang 1988; Bisgaard et al. 1988).
- FP had greater adrenal suppression at doses of 400 to 2,000 micrograms than BUD in equivalent microgram doses delivered by MDI and accompanied by mouth washing to prevent oral bioavailability (Clark et al. 1996). This confirms that there are differences in microgram potencies among preparations and that absorption through the lung can result in systemic activity.



Adapted with permission from Barnes 1995.

FIGURE 3-5d. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS

Medication	Dosage Form	Adult Dose	Child Dose	Comments
<i>Short-Acting Inhaled Beta₂-Agonists</i>				
<i>MDI</i>				
Albuterol	90 mcg/puff, 200 puffs	<ul style="list-style-type: none"> ■ 2 puffs 5 minutes prior to exercise ■ 2 puffs tid-qid prn 	<ul style="list-style-type: none"> ■ 1-2 puffs 5 minutes prior to exercise ■ 2 puffs tid-qid prn 	<ul style="list-style-type: none"> ■ An increasing use or lack of expected effect indicates diminished control of asthma. ■ Not generally recommended for long-term treatment. Regular use on a daily basis indicates the need for additional long-term-control therapy. ■ Differences in potency exist so that all products are essentially equipotent on a per puff basis. ■ May double usual dose for mild exacerbations. ■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
Albuterol HFA	90 mcg/puff, 200 puffs			
Bitolterol	370 mcg/puff, 300 puffs			
Pirbuterol	200 mcg/puff, 400 puffs			
Terbutaline	200 mcg/puff, 300 puffs			
<i>DPI</i>				
Albuterol Rotahaler	200 mcg/capsule	1-2 capsules q 4-6 hours as needed and prior to exercise	1 capsule q 4-6 hours as needed and prior to exercise	
<i>Nebulizer solution</i>				
Albuterol	5 mg/mL (0.5%)	1.25-5 mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 2-3 cc of saline q 4-6 hours	May mix with cromolyn or ipratropium nebulizer solutions. May double dose for mild exacerbations.
Bitolterol	2 mg/mL (0.2%)	0.5-3.5 mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	Not established	May not mix with other nebulizer solutions.
<i>Anticholinergics</i>				
<i>MDI</i>				
Ipratropium	18 mcg/puff, 200 puffs	2-3 puffs q 6 hours	1-2 puffs q 6 hours	Evidence is lacking for anticholinergics producing added benefit to beta ₂ -agonists in long-term asthma therapy.
<i>Nebulizer solution</i>				
	.25 mg/mL (0.025%)	0.25 mg q 6 hours	0.25-0.5 mg q 6 hours	
<i>Systemic Corticosteroids</i> (Applies to all three systemic corticosteroids)				
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	<ul style="list-style-type: none"> ■ Short course "burst": 40-60 mg/day as single or 2 divided doses for 3-10 days 	<ul style="list-style-type: none"> ■ Short course "burst": 1-2 mg/kg/day, maximum 60 mg/day, for 3-10 days 	<ul style="list-style-type: none"> ■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tabs, 5 mg/5 cc, 15 mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 25 mg tabs; 5 mg/cc, 5 mg/5 cc			

intended to be prescriptions for individual treatment. Specific therapy should be tailored to the needs and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by patient education and measures to control those factors that contribute to the severity of the asthma (see components 2 and 4).

If optimal control of asthma is not achieved and sustained at any step of care (nocturnal symptoms, urgent care visits, or an increased need for short-acting beta₂-agonists are key indications that asthma is not optimally controlled), several actions may be considered:

- Patient adherence and technique in using medications correctly should be assessed.
- A temporary increase in anti-inflammatory therapy may be indicated to reestablish control. A deterioration of asthma may be characterized by gradual reduction in PEF (approximately 20 percent), by failure of inhaled bronchodilators to produce a sustained response, by a reduced tolerance to activities or exercise, and by the development of increasing nocturnal symptoms. To regain control of asthma, a short course of oral prednisone (see figure 3-5a) is often effective. If asthma symptoms do not recur and pulmonary functions remain normal, no additional therapy is necessary. However, if the prednisone burst does not control symptoms, is effective only for a short period of time (e.g., less than 1 to 2 weeks), or is repeated frequently, the patient should be managed according to the next higher step of care.
- Other factors that diminish control may need to be identified and addressed. These factors include the presence of a coexisting condition (e.g., sinusitis), a new or increased exposure to allergens or irritants, patient or family barriers to adequate self-management behaviors, or psychosocial problems. In some cases, alternative diagnoses may need to be considered, such as vocal cord dysfunction.
- A step up to the next higher step of care may be necessary.
- Consultation with an asthma specialist may be indicated (see component 1: Initial Assessment and Diagnosis).

Intermittent Asthma

Step 1: Mild Intermittent Asthma. Short-acting inhaled beta₂-agonists taken as needed to treat symptoms are usually sufficient therapy for mild, intermittent asthma. If effective in relieving symptoms and normalizing pulmonary function, intermittent use of short-acting inhaled beta₂-agonists can continue to be used on an as-needed basis. If significant symptoms reoccur or beta₂-agonist is required for quick-relief treatment more than two times a week (with the exception of using beta₂-agonist for exacerbations caused by viral infections and for exercise-induced bronchospasm [EIB]), the patient should be moved to the next step of care.

Patients with intermittent asthma who experience EIB benefit from taking inhaled beta₂-agonists, cromolyn, or nedocromil shortly before exercise (see Exercise-Induced Bronchospasm, page 100). Cromolyn or nedocromil taken before unavoidable exposure to an aeroallergen known to exacerbate the patient's asthma may be beneficial (Cockcroft and Murdock 1987).

The Expert Panel recommends the following actions for managing exacerbations due to viral respiratory infections, which are especially common in children. If the symptoms are mild, inhaled beta₂-agonist (every 4 to 6 hours for 24 hours, longer with a physician consult) may be sufficient to control symptoms and improve lung function. If this therapy needs to be repeated more frequently than every 6 weeks, a step up in long-term care is recommended. If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of systemic corticosteroids should be considered. For those patients with a history of severe exacerbations with viral respiratory infections, systemic corticosteroids should be initiated at the first sign of the infection.

The Expert Panel recommends that a detailed written action plan be developed for those patients with intermittent asthma who have a history of severe exacerbations (see figure 4-5). Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. However, some patients with intermittent asthma experience sudden, severe, and life-threatening exacerbations. It is essential to treat these exacerbations accordingly. The patient's action plan should include indicators of worsening asthma (specific symptoms and PEF mea-

surements), as well as specific recommendations for using beta₂-agonist rescue therapy, early administration of systemic corticosteroids, and seeking medical care. Furthermore, periodic monitoring (see component 1-Periodic Assessment and Monitoring) of the patient is appropriate to evaluate whether the patient's asthma is indeed intermittent or whether a step up in long-term therapy is warranted.

Persistent Asthma

The Expert Panel recommends that patients with persistent asthma, either mild, moderate, or severe, receive daily long-term-control medication. The most effective long-term-control medications are those with anti-inflammatory effects, that is, those that diminish chronic airway inflammation and airway hyperresponsiveness. Evidence from clinical trials supports this recommendation (van Essen-Zandvliet et al. 1992; Kerstjens et al. 1992).

Step 2: Mild Persistent Asthma. The main characteristics of step 2 care are as follows:

- **Step 2 care long-term-control medication is daily anti-inflammatory medication:** either inhaled corticosteroids at a low dose (see figure 3-5b), cromolyn, or nedocromil. For children, a trial of cromolyn or nedocromil is often the initial long-term therapy due to the safety profiles of these medications.
- **Sustained-release theophylline is an alternative, but not preferred, long-term-control medication.** It is not preferred because its modest clinical effectiveness (theophylline is primarily a bronchodilator and its anti-inflammatory activity demonstrated thus far is modest) must be balanced against concerns about potential toxicity (see component 3-Medications). Theophylline remains a therapeutic option for certain patients due to expense or need for tablet-form medication.

Sustained-release theophylline is given to achieve a serum concentration of between 5 and 15 mcg/mL. Periodic theophylline monitoring is necessary to maintain a therapeutic—but not toxic—level.

- **Zafirlukast or zileuton may also be considered an alternative long-term-control medication for patients 12 years of age and older, although**

their position in therapy is not yet fully established. Initial experience in clinical trials and possible patient requirements for tablet-form medication make these new medications a therapeutic option. Further clinical experience and additional data are needed to establish the role of zafirlukast and zileuton in stepwise therapy.

- **Quick-relief medication must be available.** Inhaled short-acting beta₂-agonists should be taken as needed to relieve symptoms. The intensity of treatment will depend on the severity of the exacerbation (see component 3-Managing Exacerbations). Use of inhaled short-acting beta₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.

Step 3: Moderate Persistent Asthma. Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk/benefit outcomes. There are at least three options for initiating step 3 therapy.

- **Increase inhaled corticosteroids to medium dose.** This strategy will benefit many patients. Adverse effects, although infrequent, may arise (see component 3-Medications).

OR

- **Add a long-acting bronchodilator to a low-to-medium dose of inhaled corticosteroids.** The long-acting bronchodilator may be either a long-acting inhaled beta₂-agonist (e.g., salmeterol) (Greening et al. 1994; Woolcock et al. 1996) or sustained-release theophylline (Nassif et al. 1981); although not preferred, long-acting beta₂-agonist tablets may be considered. This approach has been shown to improve symptom control and may be especially beneficial in patients who have significant nocturnal symptoms. Improved asthma control has been demonstrated with an inhaled long-acting beta₂-agonist and a medium-dose inhaled corticosteroid compared to a doubled dose of inhaled corticosteroid (Woolcock et al. 1996), but the potential for incorrectly using long-acting inhaled beta₂-agonists as a quick-relief medication needs to be considered. The approach of adding theophylline has the potential for adverse reactions related to fluctuations in theophylline serum concentrations.