Outpatient Treatment of Adult Asthma

ERIC C. KLEERUP, MD, *and* DONALD P. TASHKIN, MD, *Los Angeles, California*

As a chronic disease with intermittent exacerbations, asthma is treated primarily in the outpatient setting by primary care physicians. Asthma is the result of complex and only partially understood interactions of respiratory, inflammatory, and neural cells and their mediators. The goals of asthma therapy are to prevent and relieve symptoms, allow normal activities of daily living, restore and maintain normal pulmonary function, avoid adverse effects from interventions, and minimize inconvenience and cost. These goals can be achieved through educating patients, assessing and monitoring asthma severity, avoiding or controlling asthma triggers, establishing an intervention plan for routine self-management and the management of exacerbations, and providing regular follow-up care. We present a stepped approach to asthma pharmacotherapy, emphasizing anti-inflammatory therapy—inhaled corticosteroids, cromolyn sodium, or nedocromil sodium—as a summary of recent national and international recommendations.

(Kleerup EC, Tashkin DP: Outpatient treatment of adult asthma. West J Med 1995; 163:49-63)

Asthma affects about 10 million Americans and results in more than 100 million days of restricted activity.[1(p317)] Despite the availability of newer drugs for its treatment, the morbidity and mortality of asthma have increased in the United States and other countries. It is uncertain if this increase in asthma morbidity and mortality has been caused by changes in the disease, the environment, or the population; unappreciated effects of the drugs used to treat asthma; or a failure to adopt recommended optimal treatment.

Asthma is difficult to define as a disease and may represent a mixture or range of causes or mechanisms. The following is an operational definition[2(p1)]:

> Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and causes an associated increase in airway hyperresponsiveness to a variety of stimuli.

National panels in the United States,[3,4] Great Britain,[5,6] Canada,[7] and Australia and New Zealand[8] and an international consensus panel[2] have recently proposed guidelines for the management of asthma.* Based on a combination of facts and the best guesses of experts, they all emphasize the importance of education, self-management, inhaled anti-inflammatory agents, and self-monitoring using peak expiratory flow (PEF) measurements. The guidelines differ somewhat in the definitions of severity and permissiveness of the formulary recommended. The degree to which the guidelines have been implemented in the general care of patients with asthma remains speculative.

*See also the editorial by H. A. Boushey, MD, "Asthma Therapy—Future Promise and Current Practice," on pages 79-80 of this issue.

Cellular Processes in Asthma

The exact mechanism(s) that causes the clinical syndrome of asthma is (are) unclear. The underlying abnormality is inflammation of the airways (cellular infiltration, edema, nerve irritation, vasodilatation) resulting in bronchoconstriction (airway smooth muscle constriction), increased mucous secretions (submucosal gland and goblet cell hyperplasia and stimulation), and airway hyperresponsiveness. A number of triggers or mediators produce asthmalike responses in susceptible persons at much lower concentrations than in "normal" subjects. These stimuli may act by triggering cascades of cell activation with subsequent cytokine release, neurologic excitation with neuropeptide or neurotransmitter release, or both. Other elements act to limit the triggered responses. Medications may act to inhibit, arrest, augment, or counteract one or more elements in the cascades. The mediators and cells involved in asthma are summarized in Tables 1 and 2. Mast cells and eosinophils play a central role in asthma.[9,10] Helper T cells orchestrate the activation and recruitment of eosinophils and mast cells through cytokines (interleukins 3, 4, and 5 and granulocyte-macrophage colony-stimulating factor).[10] Important end effectors include neuropeptides, leukotriene (C_4, D_4, and E_4) products of the 5-lipoxygenase pathway, prostaglandin (PGD_2, PGE_2, PGI_2, $PGF_{2\alpha}$) and thromboxane A_2, products of the cyclooxygenase pathway, and platelet-activating factor.[11-13] The neuropeptides are regulated by selective degradation by neutral endopeptidase,

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, Los Angeles (UCLA), School of Medicine.

Reprint requests to Eric C. Kleerup, MD, Pulmonary and Critical Care Medicine, Dept of Medicine, UCLA School of Medicine, 10833 Le Conte Ave, CHS 37-131, Los Angeles, CA 90024-1690.

ABBREVIATIONS USED IN TEXT

$FEF_{25\%-75\%}$ = forced expiratory flow between 25% and 75% of forced vital capacity
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
HPA = hypothalamic-pituitary-adrenal [axis]
MDI = metered-dose inhaler
PC_{20} = provocative concentration needed to produce a 20% drop
PEF = peak expiratory flow [rate]
PG = prostaglandin

chymase, and tryptase.[14-16] In experimental antigen challenge, the immediate reaction is initiated by nerves and inflammatory cells already present in the airways. The late-phase reaction (3 to 8 hours) is the result of new cellular infiltration and activation. These cells then release mediators, resulting in a second bronchospastic response. The activation of cells, particularly T-helper and mast cells, may persist long after the antigenic challenge has ended. The late-phase reaction results in an increase in airway hyperresponsiveness that may persist in a self-perpetuating manner or be reinforced with continual reexposure to antigen triggers.[17]

Pathophysiology of Asthma

Asthma is characterized by reversible airway obstruction and airway hyperresponsiveness. Spirometry reveals low forced expiratory flow rates (forced expiratory volume in 1 second [FEV_1], forced expiratory flow between 25% and 75% of forced vital capacity [$FEF_{25\%-75\%}$], and PEF rate) with normal or increased lung volumes (functional residual capacity, residual volume, and total lung capacity). The airway obstruction is partially or completely reversible spontaneously or with bronchodilators (improvement of ≥13% in FEV_1, ≥23% in $FEF_{25\%-75\%}$, and ≥20% in PEF rate).[18] The degree of obstruction varies with exacerbations, therapy, and time of day. Nonspecific triggers of bronchospasm (methacholine, histamine) induce it at much lower concentrations in patients with asthma than in those without. For example, the provocative concentration of methacholine necessary to produce a 20% drop (PC_{20}) in the FEV_1 is generally 10 mg per ml or less in patients with asthma and may range from 20 to more than 200 mg per ml in those without asthma. Patients with allergic rhinitis have intermediate airway reactivity with some overlap to both sides (5 to 50 mg per ml).

Other nonspecific triggers such as exercise and cold air can also produce an immediate bronchospastic reaction in asthmatic patients. Following antigen challenge, there is a late-phase influx and activation of inflammatory cells. This results in an increase in nonspecific hyperresponsiveness and predisposes the patient to subsequent episodes of bronchospasm. A circadian variation in cortisol and epinephrine levels, vagal tone, and inflammatory mediators results in a peak of bronchial reactivity and a nadir of the PEF rate between 4 AM and 8 AM and may account for episodes of nocturnal bronchospasm.[19]

Goals of Therapy

Therapy for asthma is directed at the underlying causes and mechanisms of the disease. At present, most forms of asthma are not "curable" but can be treated with great success. For most patients, asthma is a continual process with periodic exacerbations. Treatment must address both the underlying chronic inflammatory process and the overt symptoms apparent to the patient. The goals of therapy can be summarized as follows:

- Relieve and prevent symptoms.
- Allow normal activities of daily living including work (school) and exercise.
- Restore and maintain normal pulmonary function.
- Avoid adverse effects from interventions.
- Minimize inconvenience and cost.

For patients, asthma is manifested by the symptoms perceived. Most commonly, cough, wheezing, dyspnea, and chest tightness may be present episodically or continuously. Nocturnal symptoms or symptoms on awakening in the morning are common because of the diurnal variation of pulmonary concentrations, or responsiveness to endogenous catecholamines, vagal tone, and adrenocorticosteroids.[19] For any given patient, a particular symptom may be most prevalent or bothersome. Because of the frequently gradual onset of asthma and its long-term nature, it is not unusual for patients to ignore even serious symptoms as "normal" for them. Isolated cough is not unusual. A rapid relief of symptoms reduces the effects of the asthma on a patient and may be lifesaving. Preferable is the prevention of symptoms and particularly exacerbations manifested by more severe symptoms.

The prevention and the relief of symptoms allow asthmatic patients to participate fully in all physical and social activities. Patients with well-controlled asthma should not be restricted in their physical activity. With proper treatment, asthma should not result in excess loss of time from work or school or, indeed, from any activity. Clearly, poorly controlled asthma limits exercise capacity. Adequate therapy should relieve ventilatory limitations to exercise and prevent the occurrence of exercise-induced asthma. In rare cases, occupational asthma may not be controllable without a complete avoidance of inciting triggers in the workplace.

Patients' perceptions of asthma vary greatly. Symptoms may sometimes be present with unmeasurable physiologic changes, or conversely, pronounced declines in lung function may not cause any duress. A reversible obstructive ventilatory defect is the hallmark of asthma. With aggressive therapy, most patients' lung function will return to normal or near normal. Although a proportion of patients with severe asthma appear to have a component of fixed or permanent obstruction, they also have a large component that is responsive to therapy.

All medications are associated with possible adverse reactions. Some side effects are an extension of a drug's intended pharmacologic actions and are at times unavoidable if doses are to be adequate to control the disease.

TABLE 1.—*Mediators of Inflammation and Bronchospasm in Asthma*

*Effect**	*Mediator*	*Source*
Airway diameter—bronchoconstriction		
Decreased	Leukotrienes C_4, D_4, E_4	Mast cells and eosinophils
	Histamine potentiated by chymase	Mast cell degranulation
	C3a activation by tryptase	Mast cell degranulation
	Prostaglandin D_2	Mast cells
	Release augmented by neuropeptide Y	Adrenergic nerves
	Substance P	C-fiber sensory nerves
	Degraded by chymase	Mast cell degranulation
	Degraded by neutral endopeptidase	Type II epithelial cells, submucosal glands, nerves, and airway smooth muscle
	Augmented by inhibition of neutral endopeptidase	Viral or mycoplasmal infections, hypertonic saline inhalation, toluene diisocyanate (TDI)?
	Release augmented by neuropeptide Y	Adrenergic nerves
(proximal)	Acetylcholine	Cholinergic nerves
(peripheral)	Neurokinin A (tachykinin)	C-fiber sensory nerves
	Degraded by neutral endopeptidase	Type II epithelial cells, submucosal glands, nerves, and airway smooth muscle
	Augmented by inhibition of neutral endopeptidase endopeptidase	Viral or mycoplasmal infections, hypertonic saline inhalation, TDI?
	Augmented by platelet-activating factor (PAF)	Mast cells and eosinophils
	Neurokinin B (tachykinin)	C-fiber sensory nerves
Increased	Vasoactive intestinal peptide (VIP)	Cholinergic nerves
	Degraded by tryptase	Mast cell degranulation
(proximal)	Nitric oxide	Nonadrenergic noncholinergic nerves
Mucous secretion		
Increased	Substance P†	C-fiber sensory nerves
	PAF; leukotrienes C_4, D_4, E_4	Eosinophils
	Gastrin-releasing peptide (GRP)	Neuroendocrine cells in the lower airways
	Degraded by chymase	Mast cell degranulation
	VIP†	Cholinergic nerves
Vascular diameter		
Increased	VIP†; nitric oxide	Cholinergic nerves
	Substance P	C-fiber sensory nerves
	PAF; leukotrienes C_4, D_4, E_4	Eosinophils
	Prostaglandin D_2†	Mast cells
	Histamine	Mast cell degranulation
	Angiotensin II	
	Activation of angiotensin I by chymase	Mast cell degranulation
	Bradykinin (kallidin I)	
	Degraded by chymase	Mast cell degranulation
(arteriolar)	Calcitonin gene-related peptide	C-fiber sensory nerves
	Degraded by chymase	Mast cell degranulation
Decreased	GRP†	Neuroendocrine cells in the lower airways
(arteriolar)	Norepinephrine, neuropeptide Y	Adrenergic nerves
Vascular permeability—edema		
Increased	Substance P†	C-fiber sensory nerves
	PAF; leukotrienes C_4, D_4, E_4	Eosinophils
	Histamine†	Mast cell degranulation

*The effects given in parentheses indicate the localization of the effect.
†See previous entry for factors affecting levels or actions of mediator.

Fortunately, most of the medications used for the treatment of asthma have relatively few side effects and a high degree of safety.

Inconvenience and lack of immediate effect are the greatest impediments to any long-term therapy. Unfortunately, moderate and severe asthma requires some interventions that have no immediate effect. Daily medication regimens should be as simple as possible. Avoidance and environmental manipulations should also be designed with convenience and expedience in mind. The cost to patients and third-party payers must be a consideration. If patients cannot afford the treatment in terms of time or

TABLE 2.—*Cellular Chemotaxis and Activation in Asthma*

Cell	Mediator*	Source
Mast cell.....	Proliferation and differentiation	
	Interleukin (IL)-3	T cells (equivalent to murine Th-2 cells)
	Chemotaxis	
	Leukotriene E_4	Eosinophils
	Degranulation	
	Immunoglobulin (Ig) E cross-linking	Specific antigens
	Substance P	C-fiber sensory nerves
	Inhibited by vasoactive intestinal peptide*	Cholinergic nerves
Eosinophil.....	Chemotaxis and priming	
	IL-3, IL-5, granulocyte-macrophage colony-stimulating factor	T cells (equivalent to murine Th-2 cells)
	Platelet-activating factor (PAF), leukotriene E_4	Eosinophils
	Activation	
	IL-5	T cells (equivalent to murine Th-2 cells)
	PAF	Eosinophils
	Epidermal growth factor, C3b, IgG, IgA	
	IgE production	
	IL-4	T cells (equivalent to murine Th-2 cells)
	Degranulation	
	IgE cross-linking	Specific antigens

*See Table 1 entry for factors affecting levels or actions of mediator.

dollars, they will not take it. The cost of intervention must be weighed against the cost of poorly treated asthma.

Principles of Asthma Management

- Educate the patient.
- Assess and monitor asthma severity with objective measures of lung function.
- Avoid or control asthma triggers.
- Establish medication plans for long-term self-management.
- Proactively establish action plans for the self-management of acute exacerbations in partnership with the physician.
- Provide regular follow-up care.

Education

All outpatient asthma is ultimately managed by patients. Physicians must, in partnership with their patients, develop a flexible treatment plan to guide this self-management.[20] Contingencies for acute and chronic worsening and improvement must be addressed proactively. The plan may need to be changed over time. A large degree of autonomy may be given to patients, but the limitations of patients' ability to manage their asthma must also be firmly established. The latitude allowed patients is influenced by their knowledge, experience, confidence, and motivation. Patient autonomy does not absolve physicians from being responsive and available. Education is central to asthma self-management and includes both the transmission of information and training in skills (Table 3). Training patients in the self-management of asthma may require more initial physician time than the traditional paternalistic approach. Nurse educators can provide a valuable extension to physicians' educational efforts. Elements must be repeatedly reviewed and reinforced. Time must also be allotted for patients to ask questions and to express their expectations and concerns.

To understand the elements of self-management, patients require a fundamental understanding of the characteristics and causes of asthma. An explanation of the inflammatory nature of asthma is important to their understanding of the basis for the pharmacologic and nonpharmacologic interventions. Patients must understand the role of different medications in reducing inflammation and relieving bronchospasm. Patients need skill in the use of metered-dose inhalers (MDIs) and PEF meters to effectively self-manage their asthma. Physicians must also address fears regarding medications and, in particular, corticosteroids.

Patients do not have asthma in isolation. Physicians must facilitate the understanding and support of a patient's family and supervisors or teachers at work or school. This process may entail discussions with parents, spouses, supervisors, teachers, athletic coaches, and school or work health professionals. It also includes liai-

TABLE 3.—*Sample Plan for Patient Education*

Knowledge	Skills	Physician Interventions
Disease process		
Inflammation, bronchospasm, hypersensitivity		Diagnosis, assess severity, set goals of therapy
Controlling asthma triggers		
Allergens, other environmental, occupational, psychological, medications, foods	Dust proofing, panic control, stress reduction, coping skills, dietary limitations	Identify triggers
Drug therapy		
Anti-inflammatory agents, β_2-agonists, oral corticosteroids, other medications	Inhaler technique, use of spacers, nebulizers, special delivery devices, cleaning devices	Stepped therapy
Monitoring		
Peak flow, warning signs	Peak expiratory flow (PEF) meter and diary	Personal best or predicted PEF rate, green, yellow, and red zones
Management		
Treatment of exacerbations		Exacerbation treatment protocol
Complicating factors		
Sinus disease, gastroesophageal reflux, ABPA		Identification and treatment
Special topics		
Exercise, fitness, sex		

ABPA = allergic bronchopulmonary aspergillosis

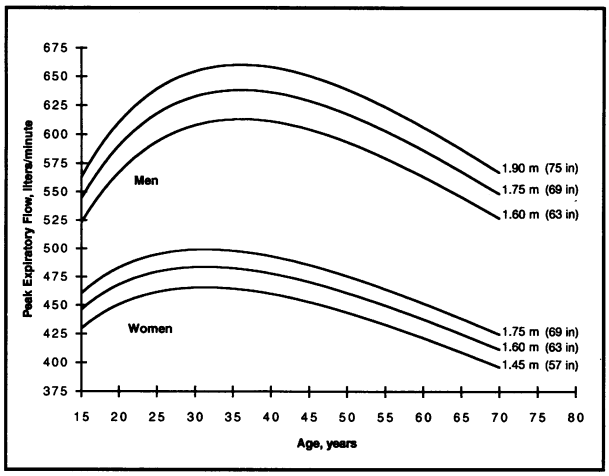

Figure 1.—Predicted normal rates are shown for peak expiratory flow. The lower 90% confidence interval (below which only 5% of the values from normal subjects would be expected to fall) is 70 to 80 liters/minute below the predicted peak expiratory flow (from Nunn and Gregg[26]).

son with other health professionals—specialists, primary care physicians, ancillary services—caring for a patient. Patients may also benefit from community support groups, which can be identified through local branches of the American Lung Association.

The control of asthma is a long-term endeavor for both patients and physicians. Feedback and measurements of progress help retain interest and enthusiasm and facilitate adjustments to management. Symptoms are most important to patients, but the importance of any particular symptom varies from patient to patient. It is useful to identify symptoms or asthma-provoking activities that are important to a particular patient and to review the response to therapy in the lessening of those specific symptoms and improved activity levels. Ultimately, symptoms are an imprecise assessment and subject to many confounding factors. Objective measurements of response are critical to assessing control. Peak expiratory flow rate monitoring is the most useful. Inexpensive and reliable, it can be performed by patients at frequent intervals to detect asymptomatic declines or improvements in lung function. Results can be compared with patients' historical best or with sex-, age-, and height-adjusted normal values (Figure 1).

Assessment of Severity

The first step in developing a plan for managing asthma is to assess the severity of the disease. Severity can be classified by clinical pattern, symptoms, need for medications and medical interventions, and severity of airflow obstruction (Table 4). These indicators of severity (or worsening of control) may not vary in concert with one another. A particular patient's disease may rank moderate in one category and mild in another. Patients with a previous near-fatal episode of asthma have a marked decrease in the perception of airway resistance (an altered sense of dyspnea). Patients with less severe asthma also have a reduced perception of dyspnea, but overlap considerably with normal subjects.[21] There is little information regarding the comparative sensitivity of these measures for detecting exacerbations, but typically for any patient an exacerbation will occur in a reproducible pattern—increased frequency of nocturnal awakenings, followed by a fall in the PEF rate, followed by increased cough, wheeze, chest tightness, or shortness of breath, followed by an increased use of inhaled albuterol. Unfortunately, patients and physicians often underestimate the degree of severity of asthma. This may lead to undertreatment and increased morbidity and mortality.

In general, previous episodes of severe asthma portend future episodes of severe asthma and increased morbidity and mortality. The recognition of risk factors for morbidity and mortality should prompt close and aggressive management. Previous life-threatening exacerbations of acute asthma resulting in respiratory failure, as evidenced by respiratory acidosis, intubation, or both, are most important.[22] Any hospital admission for asthma within the past year, particularly while the patient is receiving long-term oral corticosteroids, is an important risk factor. A number of demographic risk factors have been identified, including age (late teens to early 20s), race (African American), and socioeconomic status (inner-city, low-income). Although asthma is not caused by emotion, the following psychological factors may affect its severity and treatment: depression, alcohol abuse, recent family loss and disruption, recent unemployment, and personality disorders.[23] Barriers or lack of access to medical care, whether due to economic, social, cultural, or psychological factors, affect the control of asthma. Other risk factors that need to be assessed include noncompliance with maintenance anti-inflammatory therapy and avoidance measures, dependence on high doses or the frequent use of β_2-agonists, and recent reductions in or withdrawal from corticosteroids or other anti-inflammatory medications.

The nature and severity of symptoms reflect the severity of asthma in general. An increase in symptoms and acute exacerbations represents episodic worsening of asthma in response to exogenous stimuli—irritants, allergens, exercise, infection—or without identifiable provocation. Cough, chest tightness, wheezing, and breathlessness (with or without exercise) are common complaints. The frequency and duration ranges from rare to continual. It is important to elicit a history regarding nocturnal symptoms, awakenings from sleep, and early morning wheezing. Diurnal variability leads to increased susceptibility in the early morning. Symptoms may be induced by or present with or following exercise and result in dramatic exercise intolerance and avoidance. An important measure of asthma severity is time lost from or diminished effectiveness at work or school. Patients with more than rare absences have inadequately controlled asthma or more severe disease than previously appreciated.

The level of treatment necessary to maintain good control is another index of asthma severity. Patients with

TABLE 4.—*Assessment of Asthma Severity**

Indicator	Asthma Severity: Very Mild	Mild to Moderate	Moderate to Severe	Severe
Symptoms				
Cough, wheezing, or both	Intermittent and brief ≤2×/wk	1-2 episodes/day	4-6 episodes/day	Nearly continuous
Nocturnal asthma	≤2×/mo	2-3×/wk	Nearly nightly	Nightly
Exercise tolerance	Nearly normal	Slightly diminished	Diminished	Marked limitation
Work or school attendance	Unaffected	Occasionally affected	Substantially affected	Greatly affected
Least symptomatic days	Few clinical signs or symptoms of asthma between exacerbations	Occasional to frequent cough, wheezing, or both	Cough and low-grade wheezing often present	Cough and wheezing usually present
Treatment				
Therapy necessary to maintain control	Periodic use of bronchodilators as needed	Continuous inhaled anti-inflammatory therapy: low-dose inhaled corticosteroids, cromolyn sodium, or nedocromil sodium; occasional bursts of oral corticosteroids	Continuous inhaled anti-inflammatory therapy (usually high-dose with or without nedocromil), more frequent bursts of oral corticosteroids, may need around-the-clock bronchodilators	Continuous high-dose inhaled corticosteroids, frequent bursts of oral corticosteroids, often need around-the-clock bronchodilators, may need alternate-day or daily oral corticosteroids
Urgent treatments at MD's office or ED	Rare	<3×/yr	≥3×/yr	
Hospital admissions	None	Infrequent	≥2×/yr or requiring intubation	
Pulmonary function				
Peak expiratory flow (PEF) rate	>80% of predicted	60% to 80% of predicted	<60% of predicted	
PEF variability	<20%	20% to 30%	>30%	
Spirometry	FEV_1/FVC ratio >80%	FEV_1/FVC ratio 50% to 80%	FEV_1/FVC ratio <50%	
Response to bronchodilator	≥15% improvement in FEV_1, usually relieving any mild obstruction	≥15% improvement in FEV_1, usually to normal or near normal	≥15% improvement in FEV_1, but generally not to normal	
Methacholine sensitivity	PC_{20} 5 to 10 mg/ml	PC_{20} 1 to 5 mg/ml	PC_{20} <1 mg/ml	

ED = emergency department, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MD = physician, PC_{20} = provocative concentration needed to produce a 20% drop in FEV_1

*Modified from Sheffer,[2,3] British Thoracic Society et al,[5,6] Hargreave et al,[7] and Woolcock et al.[8] This table is a composite of national and international asthma severity grading schemes. Patients may have different degrees of severity in different categories. Select the highest level of severity as the basis for therapy.

more severe asthma require more therapy to gain and retain control. The assessment of past therapies must include medications (dose, duration, and compliance) and effectiveness (symptoms and objective measures). Whereas patients may report that β_2-agonists provide short-term relief of symptoms, their asthma may remain poorly controlled in terms of objective measures, such as the PEF rate, PEF variability, FEV_1/FVC ratio, and PC_{20}.

Monitoring of the PEF rate should be seriously considered in patients who take medications daily (moderate to severe asthma). In patients with mild asthma, it is less likely that PEF monitoring will result in a substantial reduction in morbidity or mortality.[24,25] During the adjusting of medications, patients should record the best of three PEF rates in the morning and evening at consistent times. If bronchodilators are used, PEF rates should be recorded at least before and optimally after (10 to 15 minutes) inhaling bronchodilators. After good control has been established, it may be more convenient to record only the best daily morning PEF rate. This strategy allows contin-

TABLE 5.—*Zone System of Peak Expiratory Flow (PEF) Monitoring*

Zone	Interpretation	Best PEF Rate, %	AM/PM PEF Variability, %
Green	All clear	>80	<20
Yellow	Caution	50-80	20-30
Red	Alert	<50	>30

ued early detection of asymptomatic declines in lung function that may indicate impending exacerbation or a decline in the degree of control. As evidence of good control, PEF values should be near a patient's best and near population normal values. The zone system (Table 5), analogous to the traffic light, has been developed to grade changes in PEF rates. A decline into the yellow zone may indicate the beginning of an acute exacerbation or ongoing deterioration. Therapy may be changed to increase the dose of anti-inflammatory inhalers or add a "burst" of oral corticosteroids (discussed later). Descent into the red zone indicates severe deterioration and may require emergency intervention from the physician or in the hospital emergency department. The zones are approximations and need to be tailored to each patient based on his or her history and past response to therapy. Ideally, personal best PEF rates are near population normals (see Figure 1)[26]:

Men:

$$\log_e \text{PEF (liters/min)} = 0.544 \log_e \text{Age} - 0.0151 \text{ Age} - 74.7/\text{height (cm)} + 5.48$$

Women:

$$\log_e \text{PEF (liters/min)} = 0.376 \log_e \text{Age} - 0.0120 \text{ Age} - 58.8/\text{height (cm)} + 5.63$$

Peak expiratory flow rates vary with the time of day, with the lowest values being in the morning hours (8 to 10 AM) and the highest in the afternoon (3 to 5 PM). Normal variability is probably less than 10% (4% to 18%), but may be greater than 25% (6% to 27%) in patients with stable asthma. Following an episode of asthma exacerbation, the PEF rate variability may be more than 50%.[27] The degree of PEF rate variability correlates with FEV_1 variability, the severity of asthma, and airway hypersensitivity:

$$\text{PEF Variability} = \left| \frac{\text{AM PEF} - \text{PM PEF}}{(\text{AM PEF} + \text{PM PEF}) / 2} \right|$$

Control of Asthma Triggers

Nonpharmacologic interventions should be considered in all patients being treated for asthma. In some patients, specific environmental triggers of asthma can be identified (Table 6) and avoided (Table 7). The extent to which this is possible varies from patient to patient. The simplest approach is a careful history. Patients will often associate worsening symptoms with certain activities, locations, or seasons. The ability to avoid triggers varies depending on the nature and prevalence of the trigger. The avoidance of triggers such as dust mites for two to nine months may result in a decrease in symptoms, medication use, and specific and nonspecific bronchial hyperresponsiveness.[28-30] The value of skin testing is limited without an accompanying history of a substantial response on exposure. Inhalation challenge with specific antigens is possible in some cases, but should be done only by a specialist and usually is relevant only in a research setting.

TABLE 6.—*Asthma Triggers—Inducers of Inflammation, Bronchospasm, or Both*

- Respiratory viruses
- Occupational sensitizers
  - Toluene diisocyanate, western red cedar (*Thuja plicata*) sawdust, grain dust, cotton bract
- Allergens
  - Indoors
    - House dust mites, cockroaches, pets (cats more than dogs), feathers or down, molds
  - Outdoors
    - Pollens—grasses, trees, molds
- Food additives
  - Metabisulfite
- Medications
  - Aspirin (10% to 30% of persons with asthma)
  - Other nonsteroidal anti-inflammatory drugs
  - β-Blockers (including eyedrops)
- Environmental
  - Ozone, sulfur dioxide, smog
  - Cigarette smoke, including secondhand smoke
  - Fine aerosols—household sprays, fog
  - Cold air, exercise
- Extreme emotion

Pharmacologic Therapy

Pharmacologic therapy for asthma can be divided into two broad categories: anti-inflammatory drugs and bronchodilators. Patients with mild asthma require an inhaled

TABLE 7.—*Environmental Control of Asthma*

Trigger	Control
Dust or dust mites.....	Wash bedding in hot water (58°C [137°F]) Cover mattresses and pillow cases Remove carpets from bedrooms Use acaricides or denaturing agents (tannic acid) Replace upholstered furniture and draperies Adjust humidity to <50% Filter air with high-efficiency particulate air cleaners
Molds.....	Provide adequate ventilation Clean bathrooms carefully and frequently Limit the number of houseplants Clean walls and add mold inhibitor to paint Reduce humidity to <35%
Cats.....	Keep cat out of bedroom Wash cat 3×/wk, then every 2 to 3 wk Use denaturant (tannic acid) on carpets Give cat away

TABLE 8.—*Strength and Dosage of Anti-inflammatory Medications*

Drug, μg/puff	Strength/ puff*	Manufacturer's Recommended Dose, puffs/day		Beginning of HPA Axis Suppression, puffs/day†
		Starting	Maximum	
Beclomethasone dipropionate, 42	1	6-8	20	24-30
Triamcinolone acetonide, 100	1.5-2	6-8	16†	16-20
Flunisolide, 250	2.5-3	4	8†	10-12
Cromolyn sodium, 800	<1	8	8	NA
Nedocromil sodium, 1,750	<1	8	8	NA

HPA = hypothalamic-pituitary-adrenal, NA = not applicable

*Approximate potency/puff based on limited data (from Grandgeorge et al[31]).
†May be exceeded in patients not responding adequately to lower doses.

β_2-agonist only on an as-needed basis for the relief of infrequent symptoms. They may also benefit from prophylactic therapy with a β_2-agonist, cromolyn sodium, or nedocromil sodium before exercise or an anticipated exposure to another asthma trigger. For patients with more frequent symptoms or more substantial lung function abnormality, the mainstay of asthma therapy is anti-inflammatory medication—inhaled corticosteroids, cromolyn, or nedocromil. Anti-inflammatory agents, administered on a regularly scheduled basis, treat the underlying inflammation of asthma, reducing the airway hyperreactivity and decreasing the frequency of bronchospasm and symptoms, whereas bronchodilators provide a rapid, effective relief of bronchospastic symptoms—wheezing, chest tightness, or dyspnea.

Inhaled Anti-inflammatory Agents

Airway inflammation is present even in patients with asymptomatic asthma, and the amount correlates with disease severity. Inhaled corticosteroids are nonspecific suppressors of inflammation.[3] They inhibit arachidonic acid metabolism, resulting in the decreased production of leukotrienes and prostaglandins. They also reduce the migration and activation of inflammatory cells by inhibiting cytokine production. In addition, inhaled corticosteroids increase the responsiveness of the β-receptors of the airway smooth muscle. The result is a decreased frequency of acute exacerbations, symptoms, and the need for concurrent medications. Diurnal variability in PEF rates and airway responsiveness to methacholine also decrease. Three inhaled corticosteroid preparations are currently available in the United States: beclomethasone dipropionate (Beclovent, Vanceril), 42 μg per puff; triamcinolone acetonide (Azmacort), 100 μg per puff; and flunisolide (AeroBid), 250 μg per puff (Table 8).[31]

Detectable suppression of the hypothalamic-pituitary-adrenal (HPA) axis is uncommon at doses below 1,000 to 1,500 μg (24 to 30 puffs per day) of beclomethasone or its equivalent (triamcinolone, 16 to 20 puffs per day; flunisolide, 10 to 12 puffs per day). In patients with moderate asthma, relatively low doses of inhaled corticosteroids (such as 8 puffs of beclomethasone per day or its equivalent) are usually sufficient for satisfactory asthma control. In patients with severe asthma, however, higher doses are required, and manufacturers' recommended doses are often exceeded.[32] Doses as high as 2,000 μg per day of beclomethasone (or its equivalent) have been used successfully. The optimal dose of inhaled corticosteroids is that which effectively controls asthma. Even if HPA axis suppression is present, the degree of suppression is less than that caused by a daily regimen of oral prednisone that produces a comparable control of asthma.[33] Localized infections with *Candida albicans* may occur in the mouth, pharynx, or occasionally the larynx. Clinically important infection may be treated with antifungal agents and the discontinuation of the inhaled corticosteroid. The incidence of local oral effects may be reduced by the use of a spacer and rinsing the mouth following use. Cough due to the additive oleic acid may occur with the use of Beclovent or Vanceril, but is minimized by the use of spacers. Reversible dysphonia can occur with deposition of the drugs on the vocal cords. Dermal thinning and purpura may occur particularly in older patients.[34] Laboratory studies indicate that the use of inhaled corticosteroids in high doses (≥1,500 μg of beclomethasone or its equivalent) may decrease bone density, but the implication of these small-scale findings with respect to the risk of fractures is unclear. Results in patients are less clear. Inhaled corticosteroids may also cause nausea, vomiting, diarrhea, headache, and sore throat. Patients with unstable or severe disease may benefit from three- or four-times-a-day dosing. Stable patients with mild or moderate asthma, however, may have improved compliance and equivalent effectiveness with twice-a-day dosing. Frequent exacerbations indicate a failure of the regimen and are an indication to intensify the long-term therapy.

Before increasing inhaled corticosteroid doses, it is important to review inhaler technique and compliance. In one study, 45% of patients were estimated to be taking less than 51% of the prescribed doses of inhaled corticosteroids.[35] After asthma control is achieved, a stepwise decrease in anti-inflammatory therapy may be possible and is advisable. In a recent Finnish study, 74% of patients with mild asthma remained stable after a two-thirds reduction in the dose of inhaled corticosteroids after two years at the higher dose.[36] The ideal dose of inhaled corticosteroids is the minimum dose necessary to achieve and maintain the goals of therapy.

Cromolyn and nedocromil are nonsteroidal but less potent anti-inflammatory agents (see Table 8). Cromolyn inhibits mediator (histamine) release and degranulation from mast cells. It also may possess tachykinin (substance P and neurokinin B) antagonist properties.[37] Nedocromil inhibits the release of histamine and PGD_2 from mast cells[38] and the mobilization of neutrophils and eosinophils.[39] Nedocromil also inhibits neural impulse propagation in the sensory C fibers of the airway wall, resulting in decreased neuropeptide release.[40] It has a greater protective effect than cromolyn against bron-

chospasm induced by nonallergenic stimuli, such as cold air, sulfur dioxide, metabisulfite, and hypertonic saline solution.[41] Cromolyn sodium (Intal) is available as an MDI delivering 800 μg per puff (as well as a dry-powder inhaler and a solution for use with a powered nebulizer). Nedocromil sodium (Tilade) is available as an MDI delivering 1.75 mg a puff. Nedocromil may be slightly more effective than cromolyn.[42] Nedocromil (2 puffs 4 times a day) is about equivalent to beclomethasone (2 puffs 4 times a day).

Because both nedocromil and cromolyn have favorable side-effect profiles and no HPA axis suppression, they should be considered for use in patients with mild to moderate asthma. No studies have been done of the effectiveness of higher doses. If asthma control has been achieved, a reduction in the frequency of dosing from four to three or two times a day may be attempted several weeks after the initiation of therapy. Prophylactic dosing with cromolyn or nedocromil is also useful to prevent symptoms induced by exercise or trigger exposure; however, inhaled β_2-agonists are more effective for the prevention of exercise-induced bronchospasm. Concomitant therapy with nedocromil and inhaled corticosteroids may permit a reduction in the dose of inhaled corticosteroids in patients requiring high doses of the latter.[43] Nedocromil and cromolyn are generally well tolerated, but occasionally their use is associated with gastrointestinal symptoms (nausea, vomiting, dyspepsia, or abdominal pain) more often than is placebo. An unpleasant taste, throat irritation, or dryness may also result in discontinuation or poor compliance. Intal (cromolyn) infrequently causes reproducible bronchospasm, nasal congestion, cough, or laryngeal edema.

Oral Anti-inflammatory Agents

Oral corticosteroid therapy can be divided into two types—"burst" and long-term (ongoing). Burst regimens of 7 to 14 days are appropriate for acute exacerbations and poorly controlled chronic asthma, either at the initiation of therapy or when the response to long-term anti-inflammatory therapy is inadequate. Little residual effect on the HPA axis occurs after burst therapy, and tapering is not necessary to prevent adrenal insufficiency. During a burst regimen, however, it is often useful to taper the corticosteroid dose to evaluate the effect of withdrawal on a patient's asthma. Gradual withdrawal allows the early detection of a relapse of asthma symptoms or objective declines in airflow without catastrophic exacerbations.

The following is an example of a burst regimen: prednisone each morning: 60 mg on days 1 to 3, 50 mg on day 4, 40 mg on day 5, 30 mg on day 6, 20 mg on day 7, 10 mg on day 8, and stop (dispense 33 tablets, 10 mg each). Divided doses (two thirds in the morning, one third in the evening) may be used with daily doses of more than 30 mg. In general, the requirement for a prednisone burst necessitates a temporary or long-standing increase of a patient's inhaled anti-inflammatory regimen. Every effort should be made to minimize the long-term use of oral corticosteroids. For an equivalent degree of asthma control, the daily use of oral corticosteroids causes considerably more systemic side effects than a daily use of inhaled corticosteroids. Continual efforts should be made to reduce oral corticosteroid doses by increasing the dose of inhaled corticosteroids. Patients without satisfactory control of their asthma who are taking more than 10 mg of prednisone daily or 20 mg every other day should be referred to a specialist with this explicit goal. In patients previously on long-term maintenance therapy with oral corticosteroids, the withdrawal of oral corticosteroids may result in adrenal insufficiency for as long as a year. This complication is not prevented by the use of inhaled corticosteroids. During adrenocortical stress, including that caused by surgical therapy, oral corticosteroid therapy may be necessary to prevent symptomatic hypoadrenalism.

Bronchodilators

The major role of bronchodilators is the temporary relief of symptoms primarily due to bronchoconstriction. Regularly scheduled, around-the-clock use of short-acting or long-acting bronchodilators may mask the severity of asthma, resulting in undertreatment of the underlying inflammation.

Short-acting selective β_2-agonists are ideal for the initial control of bronchospasm and the prevention of exercise-induced bronchospasm. Such agents include albuterol sulfate (Proventil, Ventolin), terbutaline sulfate (Brethaire), metaproterenol sulfate (Alupent), bitolterol mesylate (Tornalate), and pirbuterol acetate (Maxair), all available as MDIs. For mild symptoms, two puffs as needed should be sufficient. Frequent use indicates a more serious exacerbation or poor control. When used in higher doses, all "selective" β_2-agonists will exhibit β_1-agonist effects, most often manifested by tachycardia in addition to tremor or anxiety (both β_2-agonist effects). Less selective β-agonists (epinephrine bitartrate [Primatene], isoproterenol [Isuprel] hydrochloride, and isoetharine mesylate [Bronkometer]) may cause a higher degree of cardiac side effects. In large doses, the use of inhaled β_2-agonists may result in a slight lowering of the serum potassium level.

Ultralong-acting bronchodilators—such as salmeterol xinafoate (Serevent) (a recently released, ultralong-acting inhaled β_2-agonist with a ≥12-hour duration of bronchodilation), controlled-release oral albuterol, and theophylline—all relieve bronchospasm for extended periods of time. Their role in ongoing therapy for asthma is unclear. In patients with mild disease, they may mask an increasing severity of symptoms that would be more appropriately treated with inhaled anti-inflammatory agents. In patients with poorly controlled moderate or severe disease, they may lull the patient and physician into accepting less-than-optimal anti-inflammatory therapy. Nonetheless, around-the-clock bronchodilator therapy may be required in addition to maximal doses of inhaled corticosteroids (with or without nedocromil) for the adequate control of symptoms in patients with moderate to severe asthma. Ultralong-acting bronchodilators (sus-

tained-release theophylline or twice-a-day salmeterol inhaler) provide more consistent around-the-clock bronchodilation than regularly scheduled (4 times a day or every 4 hours), short-acting β_2-agonists such as albuterol and may be more effective in preventing nocturnal asthma symptoms.[44,45] Salmeterol also has a long duration (≥8 hours) of protection against exercise-induced bronchospasm. In some physically active young patients with mild asthma who frequently have exercise-induced bronchospasm, salmeterol taken in the morning may provide superior prophylaxis over repeated doses of a short-acting β_2-agonist before each period of exercise.

Inhaled ipratropium bromide (Atrovent) is a second-line choice for acute bronchodilator therapy in patients with asthma who are intolerant of side effects associated with β_2-agonist therapy. The onset of action is somewhat slower (peak response, 20 to 30 minutes; 50% of maximal response, 3 to 4 minutes) than that of a β_2-agonist. The quaternary ammonium structure results in poor absorption and almost no systemic atropinelike effects. It is unclear if the maximal response achieved after a high dose of a β_2-agonist or ipratropium or the combination of the two is greater. In general, however, two puffs of either a β_2-agonist or ipratropium give a submaximal response, and further improvement may be seen with an additional dose of either the same drug or the other drug. Ipratropium may produce dry mouth and a bad taste. A closed-mouth technique is recommended for the MDI to prevent spray in the eyes, causing temporary blurring of the vision.

Theophylline and Aminophylline

With the emphasis on anti-inflammatory drugs for ongoing asthma therapy and fast-acting inhaled β_2-agonists for initial treatment, theophylline has been relegated to a minor role in the treatment of asthma. Theophylline does not provide notable anti-inflammatory effects in tolerable pharmacologic doses. Superior bronchodilation is provided by β_2-agonists or anticholinergics without the attendant side effects. In acute asthma exacerbations, the addition of intravenous aminophylline to treatment with an inhaled β_2-agonist and intravenous corticosteroids increases the risk of side effects but does not improve objective measures of airflow. Adverse effects from theophylline may be seen at therapeutic levels (8 to 15 μg per ml), and severe side effects are common at higher levels. Adverse effects include nausea, vomiting, dyspepsia and gastroesophageal reflux, diarrhea, intestinal bleeding, aspiration, tachycardia, insomnia, headaches, irritability, life-threatening arrhythmias, seizures, cardiac arrest, and death. Interindividual and intraindividual variations in metabolism and absorption of theophylline are complicated by interactions with common drugs. Clearance is increased by the addition of phenobarbital, phenytoin, intravenous β-agonist (albuterol sulfate, isoproterenol), furosemide, and cigarette or marijuana smoking. Clearance is reduced with the use of erythromycin, quinolones, isoniazid, cimetidine, calcium channel blockers, allopurinol, oral contraceptives, caffeine, and influenza vaccine and with the presence of liver disease, congestive heart failure, fever, or pregnancy. The narrow therapeutic window necessitates careful monitoring, including serum theophylline levels. If theophylline is used at all, objective evidence of benefit must be shown beyond that achieved with primary lines of treatment in any patient.

Delivery Systems

Various delivery systems are available for asthma medications (Table 9). Inhalation is the preferred route because it delivers high concentrations of a drug directly to the airways, thus minimizing systemic effects for equivalent airway effects. Adjuncts such as spacers further reduce the systemic absorption and local side effects by reducing oropharyngeal deposition. With spacers, larger particles that would usually affect the oropharynx affect the spacer, and the smaller respirable particles (≤5 μm median aerodynamic diameter) slow in velocity, resulting in less throat irritation. The standard MDI requires some training and hand-breath coordination to use effectively. Patients who are extremely dyspneic, with arthritic hands, or with poor hand-breath coordination may have particular difficulties. They may benefit from the use of breath-activated MDIs (pirbuterol [Maxair Autohaler]), dry-powder inhalers, or inhalation solutions by nebulizer. Long-acting oral or inhaled bronchodilator therapy may be useful in patients with severe asthma for the control of symptoms not relieved by intensive anti-inflammatory therapy. Subcutaneous and intravenous bronchodilator preparations are potentially useful in the treatment of patients with acute exacerbations in an emergency department or hospital, but they are impractical for ongoing care.

Immunotherapy

In contrast to its efficacy in allergic rhinitis, the role of immunotherapy in asthma is unclear. In carefully selected cases, a few specific well-defined antigens (grass pollen, house dust mite, *Alternaria* species) may provide an antigen-specific reduction in sensitivity. This mild benefit must be weighed against the potential for systemic reactions (5% to 30%), including anaphylaxis, and the cost and inconvenience of weekly physician visits.[46,47]

Experimental Anti-inflammatory Therapy

The goal of the use of most experimental anti-inflammatory agents is to reduce the dependence on oral corticosteroids, particularly in patients requiring treatment with high doses of oral prednisone (>10 mg per day or 20 mg every other day) and maximal doses of inhaled corticosteroids. Troleandomycin, methotrexate, gold salts, and cyclosporine have all been studied.[48]

Troleandomycin, a macrolide antibiotic, prolongs the elimination of methylprednisolone sodium succinate. Although the dose of methylprednisolone may be reduced, the corticosteroid-associated side effects are not attenuated, at least initially.[49] A few open-label studies have shown that some troleandomycin-responsive patients

TABLE 9.—*Available Preparations of Selected Asthma Medications*

Drug	Metered-dose Inhaler (MDI)	Breath-activated MDI	Dry Powder Inhaler	Inhalation Solution	Oral	Oral Controlled Release	Sub-cutaneous	Intra-venous
Beclomethasone dipropionate	X	--	--	--	--	--	--	--
Triamcinolone acetone	X	--	--	--	--	--	--	--
Flunisolide	X	--	--	--	--	--	--	--
Cromolyn sodium	X	--	X	X	--	--	--	--
Nedocromil sodium	X	--	--	--	--	--	--	--
Bronchodilators								
Epinephrine	X	--	--	--	--	--	X	--
Albuterol	X	--	X	X	X	X	--	--
Terbutaline	X	--	--	--	X	--	X	--
Metaproterenol	X	--	--	X	X	--	--	--
Bitolterol	X	--	--	X	--	--	--	--
Pirbuterol	X	X	--	--	--	--	--	--
Theophylline or aminophylline	--	--	--	--	X	X	--	X

subsequently may achieve acceptable control of asthma symptoms and the resolution of cushingoid features with relatively low doses of alternate-day methylprednisolone,[50] although a recent double-blind, placebo-controlled study failed to show any benefit.[51]

Methotrexate, a folic acid analogue, inhibits thymidylate synthesis, resulting in an antiproliferative effect. It appears to inhibit interleukin 1 production, histamine release from basophils, and neutrophil chemotaxis by C5a and leukotriene B_4. Recent studies have demonstrated no significant difference between methotrexate use and that of placebo in reducing oral corticosteroid dosage.[51,52] It is possible, however, that a small subset of patients responds to the use of methotrexate.[52] Mild side effects include nausea, diarrhea, headache, rash, and elevated liver enzyme levels (as much as 40% of patients). Severe side effects include liver fibrosis (as much as 5%), methotrexate pneumonitis or fibrosis (3% to 5%), and opportunistic infections.

Gold salts appear to inhibit the release of histamine and leukotriene C_4 from mast cells and basophils and appear to have a range of other immunosuppressive effects. Studies are plagued by withdrawals due to side effects, but other patients often show a slight reduction in corticosteroid use.[53-55] The side effects are common (20% to 37%) and include proteinuria, dermatitis, stomatitis, nausea, and diarrhea.

Cyclosporine prevents mast cell degranulation and inhibits the transcription of interleukins 2, 3, 4, and 5 and T-cell activation. The addition of cyclosporine to a regimen of steroid-dependent asthma appears to improve PEF rates and FEV_1 values and to reduce exacerbations compared with placebo.[56] This drug has not been well studied for its steroid-sparing effect. Side effects include nephrotoxicity, hypertrichosis, paresthesias, headaches, hypertension, and herpes zoster.

Frequent monitoring and intensive intervention, especially with inhaled corticosteroids, are often effective in reducing the dose of oral corticosteroids, as evidenced by the pronounced response to placebo in studies of alternative anti-inflammatory agents. The use of experimental anti-inflammatory agents currently can only be recommended in rare cases after exhaustive attempts have been made to reduce oral corticosteroid doses using inhaled corticosteroids in maximal doses and other conventional therapies.

Stepped Therapy

The initiation of therapy must be individually tailored depending on the disease severity (Figure 2). Following the initiation of treatment at a level appropriate for a patient's severity, stepwise increases or decreases in therapy may be indicated. The presence of signs, symptoms, or abnormalities of objective measures of lung function (PEF rate, PEF variability, or spirometry) may indicate a need to initiate or increase anti-inflammatory therapy. A good clinical response and normal or near-normal objective measures of lung function may allow reductions in anti-inflammatory therapy. In patients with moderate to severe asthma, initial treatment appropriate for an acute exacerbation followed by aggressive initial maintenance therapy and gradual increments or reductions in therapy as tolerated is appropriate. In more mild cases, initial low-dose maintenance therapy may be instituted, followed by gradual stepwise increases or decrements as appropriate. Patients with mild asthma may also use a short-acting β_2-agonist (or cromolyn or nedocromil) as prophylaxis before exercise or anticipated exposure to asthma triggers. In selected cases of severe asthma, around-the-clock bronchodilators (short- or preferably long-acting oral or inhaled β_2-agonists or sustained-release theophylline) may be necessary to control frequently recurring symp-

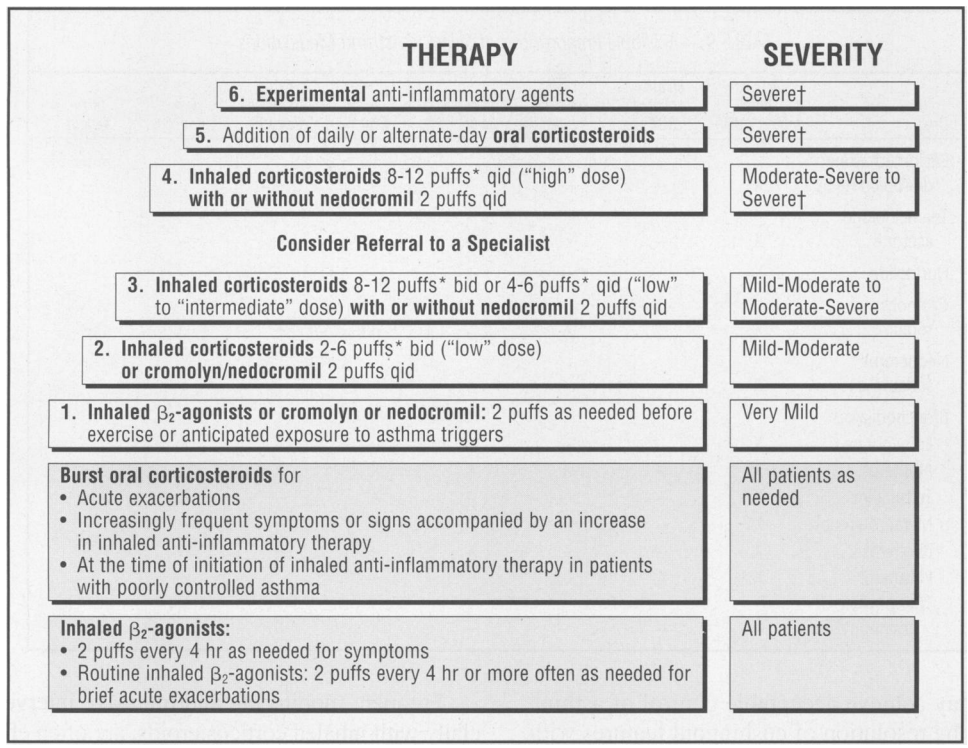

Figure 2.—Stepped therapy for asthma is shown: As asthma increases in severity, patients proceed up the steps from 1 to 6. With improvement, decreases in therapy may be possible and should be attempted on a regular basis (from Sheffer,[2,3] British Thoracic Society,[5,6] Hargreave et al,[7] and Woolcock et al[8]). *Doses of inhaled corticosteroids are given in terms of beclomethasone dipropionate: 2.5 to 3 puffs of beclomethasone are approximately equivalent to 1.5 to 2.5 puffs of triamcinolone acetonide or 1 puff of flunisolide. †Patients with severe asthma may require around-the-clock maintenance bronchodilators to control symptoms, preferably either a sustained-release oral bronchodilator (theophylline or albuterol) or an ultralong-acting inhaled bronchodilator (salmeterol). bid = twice a day, qid = 4 times a day

toms, especially nocturnal symptoms, that persist despite maximal anti-inflammatory therapy. Patients should always have medications available for the treatment of acute exacerbations, usually a short-acting β_2-agonist (which may be used at frequent intervals, if necessary, during the exacerbation) and oral prednisone. Asthma in adults will often continue to be present to a greater or lesser extent for life. Constant vigilance is required for both the recognition of deteriorating control of asthma and opportunities for reducing pharmacologic therapy when the disease is well controlled.

Acute Exacerbations

Acute exacerbations represent either the failure of ongoing therapy, the effects of intercurrent viral upper respiratory tract infections, or unexpected exposure to patient-specific triggers of asthma. Patients must be given clear guidelines—preferably in writing—for both the assessment and treatment of acute exacerbations and, in particular, when to seek a higher level of care such as a hospital emergency department. The goals for the evaluation and treatment of acute exacerbations can be summarized as follows:

- Assess the severity of an exacerbation.
- Relieve symptoms.
- Restore lung function.
- Prevent recurrence.

Patient guidelines for assessing the severity of exacerbation must be individually tailored. The first indication of an exacerbation is usually either an increase in symptoms or a decline in the PEF rate below the patient's "normal" range. The zone system (see Table 5) uses the PEF rate to provide an objective measurement of exacerbation severity. Exacerbations identified earlier, in the "yellow" range, are more easily treated. Well-instructed patients may treat many exacerbations at home alone or in consultation with their physicians. Patients should seek evaluation and treatment in an emergency department if an attack is characterized by any of the following:

- Rapid onset.
- Previous history of severe attacks.
- Peak expiratory flow rate less than 50%.
- Lack of response to initial therapy.

The pharmacologic treatment of acute exacerbations is an intensification of long-term bronchodilator and anti-inflammatory therapy. Initial therapy with a short-acting β_2-agonist such as albuterol is directed at the rapid relief of bronchospasm. An example is two to four puffs of al-

buterol every 20 minutes for three doses. This is followed by regular, around-the-clock use of β_2-agonists every three to six hours for as long as two days or until the episode resolves. A lack of appropriate response is indicated if the initial response is not prompt and sustained for at least three hours, there is further deterioration in symptoms or the PEF rate, or frequent administrations of β_2-agonists are required for longer than 48 hours. The key to resolving exacerbations is to reduce inflammation. For relatively mild and transient episodes, removal of the trigger and the lapse of time may be sufficient if the acute bronchospasm is relieved by the use of β_2-agonists. For mild to moderate attacks or a gradual loss of ongoing control, a temporary or long-term increase in the doses of inhaled corticosteroids may be adequate. Many moderate to severe exacerbations are best treated initially with a short course (burst) of oral prednisone, however. The failure of symptoms and the PEF rate to further improve three to six hours after oral corticosteroids are taken indicates an inadequate response, and consideration should be given to emergency department evaluation.

Critical to the evaluation and treatment of exacerbations is preventing recurrences. It may be possible to avoid newly identified triggers, or at least to recognize the effects earlier. A review of compliance and inhaler technique is important before increasing anti-inflammatory doses. Exacerbations without a defined trigger or in which the trigger is mild or unavoidable indicate a need for an increase in (or initiation of) anti-inflammatory therapy.

Complicating Factors

Many complicating factors may make asthma difficult or impossible to control. Compliance with the patient's asthma management plan and MDI technique must be reviewed meticulously in any patient with suboptimally controlled asthma or an exacerbation. The signs and symptoms of asthma are nonspecific and may be mimicked by a variety of diseases not necessarily responsive to antiasthma medications (Table 10). A number of coexistent diseases, including gastroesophageal reflux, rhinitis and sinusitis, and allergic bronchopulmonary aspergillosis, make asthma more difficult to control. Pregnancy and surgery require planning and careful perievent management of asthma. Each patient, at evaluation and at reevaluation following an exacerbation, should have consideration given to these possibly complicating factors.

Inhaler technique greatly affects the delivery of drug to the lungs and, therefore, the efficacy of therapy. Simply asking patients to demonstrate their use of an inhaler reinforces the importance of technique to them and provides an opportunity to correct any deficiencies. Compliance is a complex interplay of patients' perceptions of the risks, benefits, and cost (time, convenience, and dollars) of therapy. Understanding a patient's perceptions of the risks, benefits, and cost can help improve compliance with the current regimen, guide modifications to improve compliance, or direct educational interventions. Of particular concern are patients whose decrement in lung function greatly exceeds their perceived symptoms.

TABLE 10.—*Disorders Mimicking Asthma*

Laryngeal dysfunction
Mechanical upper airway obstruction
Congestive heart failure ("cardiac" asthma)
Pulmonary embolism
Cigarette-related COPD with hyperreactive airways
Pulmonary infiltrates with eosinophilia
Viral bronchiolitis or *Mycoplasma* species infection

COPD = chronic obstructive pulmonary disease

Gastroesophageal reflux may trigger severe bronchospasm and increase airway hyperresponsiveness. The reflux of acidic fluid into the upper esophagus or with aspiration into the trachea is a common cause of refractory asthma. Patients with serious reflux proved by 24-hour esophageal pH probe may not have heartburn or other reflux symptoms. Neutralizing the stomach contents by administering a histamine H_2-blocker (cimetidine, ranitidine, or the like) or a proton pump inhibitor (omeprazole), with or without a prokinetic agent, removes the insult, but reductions in hyperresponsiveness and the severity of asthma may take as long as six months.

Rhinitis and particularly sinusitis may also make asthma difficult to control. Recurrent postnasal drip irritates the larynx and trachea and increases airway hyperresponsiveness. The treatment of sinusitis, rhinitis, or both may result in dramatic improvements in the control of asthma, but seldom eliminates asthma.

Allergic bronchopulmonary aspergillosis is caused by an aggressive immune response to the noninvasive growth of *Aspergillus* species in the airways. The intense local inflammatory response may result in severe asthma that requires high doses of oral corticosteroids for even marginal control. Patients typically present with episodes of fever, wheezing, productive cough, minimal hemoptysis, shortness of breath, leukocytosis, and sputum and blood eosinophilia, particularly during the winter months. Patients may expectorate brownish plugs or flecks (56%) and, occasionally, bronchial casts. The syndrome is characterized by asthma with proximal bronchiectasis, peripheral blood eosinophilia ($>1.0 \times 10^9$ per liter [1,000 per mm^3]), greatly elevated serum immunoglobulin E levels (>2,400 mg per liter [1,000 units per ml]), transient or fixed pulmonary infiltrates, immediate and intermediate skin reactivity to *Aspergillus* antigen on prick or intradermal testing, and precipitating antibodies against *Aspergillus* antigen.

Asthma in Pregnancy

The preparation for pregnancy should begin well in advance to achieve good control of a patient's asthma. In about equal proportions of patients, asthma will improve, worsen, or remain unchanged during pregnancy. The same stepped approach used for general asthma care is appropriate to care during pregnancy.[4] No therapy has been proved absolutely safe for use during pregnancy. For mild asthma treated with β_2-agonists as needed, reassuring clinical experience exists with terbutaline, albuterol,

and metaproterenol. For patients requiring anti-inflammatory therapy, the use of beclomethasone or cromolyn is supported by human studies and long experience. Bursts of oral corticosteroids are appropriate for the routine care and treatment of exacerbations because corticosteroid use is preferable to the deleterious physiologic effects of withholding treatment.

Preparing for Surgical Therapy

Achieving optimal asthma management before a surgical procedure and general anesthesia is preferable. Patients with poor asthma control or who are experiencing an exacerbation should receive a burst course of corticosteroids in an effort to optimize asthma control, if possible, before an operation. Intubation, anesthesia, and mechanical ventilation may trigger asthma exacerbations. Prophylactic intervention may avoid or reduce complications. Patients with mild asthma may require only the routine use of β_2-agonists before, during, and immediately after surgical therapy. Patients with moderate or severe asthma may benefit from a brief oral (or parenteral when the patient cannot take anything by mouth) course of corticosteroids, in addition to around-the-clock β_2-agonists. A patient's usual regimen of inhaled corticosteroids should be resumed as the oral corticosteroid therapy is tapered or discontinued. For patients treated with daily corticosteroids for more than three weeks within the past year or with the long-term use of high doses of inhaled corticosteroids (such as beclomethasone, ≥1,500 μg per day, or its equivalent), stress-dose corticosteroid therapy for possible adrenal suppression is indicated regardless of the need for the control of asthma.

Referral to Specialists

Asthma can be well managed by interested primary care physicians. Consultation with an asthma specialist, usually a pulmonologist, allergist, or immunologist, is prudent if any of the following are present:

- Doubt regarding the diagnosis of asthma.
- Complicating or contributory factors.
- Inability to control asthma or need for daily or high-dose alternate-day oral corticosteroids.
- Admission to a hospital or recurrent visits to an emergency department for asthma.

After a simple consultation or a period of stabilization, it is reasonable for patients to return to their primary care physician for continuing care. Specialist and primary care physicians should develop a plan for both ongoing therapy and the treatment of acute exacerbations, which can be carried out by the physician providing continuing care.

Looking to the Future

Further elucidation of the cellular and molecular mechanisms of asthma should lead to the development and refinement of pharmacologic interventions. A number of newer inhaled corticosteroids—fluticasone propionate, budesonide—used outside the United States show excellent promise for delivering medication with higher topical potency and lower systemic side effects. Inhibitors of arachidonate 5-lipoxygenase and antagonists of the end products of the leukotriene pathway such as leukotrienes D_4 and E_4 show promise as antiasthma agents. Cyclooxygenase inhibitors or thromboxane and prostaglandin antagonists (thromboxane A_2, PGD_2, or $PGF_{2\alpha}$) also have promise, but are less well developed. Neuropeptide receptor antagonists, platelet-activating factor inhibitors, and pharmacologic or immune modulation of T cells all have theoretical antiasthma actions that may be exploited in the future.

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