Goals of Asthma Management*
A Step-Care Approach

Roger C. Bone, MD, FCCP

The past 15 years have seen a rise in mortality and morbidity resulting from asthma, despite a concurrent rise in general knowledge about the disease. The step-care strategy recognized these changes in its approach to asthma management; however, this approach should be used only with attempts to control environmental allergens. Step-care therapy requires that patients be categorized by the severity of illness. Step-one therapy is used for mild, infrequent symptoms and involves treatment based primarily on inhaled bronchodilators. Step-two therapy is instituted in all asthmatics except the mildest cases; it involves treatment by inhaled corticosteroids, cromolyn, or nedocromil. Step-three treatment targets cases of severe asthma through the use of oral corticosteroids. In all phases of treatment, however, it should be remembered that patient education is of critical importance. Education improves patient compliance and is critical to the successful treatment of asthma. (CHEST 1996; 109:1056-65)

**Key words:** airway hyperresponsiveness; bronchodilator; circadian rhythm; cytokines; inflammatory response; mediators

Pathophysiology

Asthma occurs in phases because the inflammatory response is composed of a multitude of mediated interactions, each with its own time frame. The acute asthmatic response is characterized by wheezing and coughing. The corresponding response in terms of inflammation consists of interactions between an allergen and a mast-cell-bound IgE molecule. This activates the mast cell, which then releases histamine and other mediators of inflammation resulting in smooth muscle contraction, increased vascular permeability, and vasodilation. This early response is rapid, occurring within minutes, and attracts other inflammatory cells that join in the response. Glandular activity is also stimulated by this inflammatory cascade, resulting in the secretion of mucus into the airways. The mucus causes coughing and may result in dyspnea if the ob-

*From the Medical College of Ohio, Toledo.

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Reprint requests: Dr. Bone, President and Chief Executive Officer, Professor of Medicine, Medical College of Ohio, 3000 Arlington Avenue, Toledo, OH 43614
The long-term result of this inflammation is a cellular infiltrate consisting of eosinophils, neutrophils, and basophils, all of which release additional mediators of inflammation. The number of lymphocytes and monocytes within the lung increase within 12 h. These cells may be particularly important in bringing about the chronic form of inflammatory response in asthma through the release of cytokines and arachidonic acid-derived mediators. This activity takes place in a time frame of from 2 h to several days and longer following activation of the mast cells by antigen. This is called the late-phase response.

One important effect of this inflammation is the sensitization and disruption of the airway lining, which can, in turn, cause irritation with reflex coughing. This nonspecific bronchial reactivity may underlie such forms of asthma as exercise- and cold-induced asthma and other responses to environmental changes, inhaled irritants, and infectious stimuli. Additionally, this long-term response leaves the tissues sensitized and any further interaction with allergens may cause a dramatic response, termed hyperresponsiveness. The terms extrinsic and intrinsic have long been used to define asthma, the former being associated with high circulating IgE levels and a positive response to skin pricks with allergens. Although our current understanding of asthma does not allow us to fully explain this difference, it could be that these two forms are actually different phases of the same disease. Systemic responsiveness may be lost with age, turning the extrinsic into the intrinsic form of the disease.

Long-term inflammation is also associated with another detrimental response—that of fiber deposition. Inflammation mediators have powerful effects on a variety of cell types, including that of inducing the genes for various connective tissue fibers. Although this may be appropriate in areas where severe tissue destruction has occurred, it is not advantageous in chronic asthma. Fibrosis, together with smooth muscle hypertrophy, thickens the airway walls and causes fur-

### Table 1—How Step-Care Affects the Early-Phase and Late-Phase Pulmonary Response*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Candidates</th>
<th>Drug Therapy</th>
<th>Early-Phase Response</th>
<th>Late-Phase Response</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step-one: Relieve acute symptoms</td>
<td>Patients with mild intermittent asthma</td>
<td>β2-Adrenergic agents, albuterol, bitolterol, mesylate, metaproterenol sulfate, pirbuterol acetate, terbutaline sulfate</td>
<td>Rapid reversal of acute symptoms; relax smooth muscle</td>
<td>Do not prevent inflammation; do not reduce or reverse airway hyperresponsiveness</td>
<td>Reverse mediator-induced bronchospasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticholinergic agent: ipratropium bromide</td>
<td>Produces bronchodilation by inhibiting vagally mediated bronchoconstriction</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aerosol corticosteroids: Beclamethasone dipropionate, flunisolide, triamcinolone acetonide</td>
<td>Effective therapy</td>
<td>Prevent and effectively manage inflammation; inhibit mucus release; reduce or reverse AHR</td>
<td>Inhibit inflammatory cell influx; stimulate production of lipocortin, thereby preventing formation of prostaglandins and leukotrienes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: Cromolyn sodium, nedocromil</td>
<td>Prophylactically block inflammation</td>
<td>Block prophylactically; reduce AHR</td>
<td>Stabilize and prevent mast cell degranulation</td>
</tr>
<tr>
<td>Step-two: Protect against and manage inflammation with agents that have few toxic effects</td>
<td>Patients with other than the mildest case of asthma; step-two therapy should probably be used in all patients with asthma</td>
<td>Oral corticosteroids: Methylprednisolone, prednisolone, prednisone</td>
<td>Ineffective</td>
<td>Prevent and manage inflammation; inhibit edema formation and mucus release; reduce or reverse increased AHR</td>
<td>INhibit inflammatory cell influx; stimulate production of lipocortin, thereby preventing formation of prostaglandins and leukotrienes</td>
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<td></td>
</tr>
<tr>
<td>Step-three: Control severe exacerbations</td>
<td>Patients with asthma refractory to step-one and step-two agents</td>
<td></td>
<td></td>
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</tr>
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</table>

*Theophylline can be used as an adjunct to step-one or step-two therapy. Salmeterol can be added as an adjunct to step-two therapy. Adapted with permission from Bone RC. Step care for Asthma. Journal of Challenges in Asthma 1992; 1:1-8.
There is a strong circadian rhythmicity to the severity of asthma that exhibits its worst symptoms between 3 and 5 AM. A form of asthma termed nocturnal asthma, in which the patient awakes during the night with breathing difficulties, is often seen. Pulmonary function values in nocturnal asthma may vary by as much as 50% between 4 PM and 4 AM. During the night, increased numbers of inflammatory cells can be found in the BAL of patients with nocturnal asthma. This form of disease may be responsible for half of all asthma deaths. Although the cause of these circadian swings in severity is not fully understood, there is undoubtedly input from a variety of different factors. These swings may have direct and indirect effects on the airways.

Patients with asthma may have disease of widely varying seriousness; symptoms may range from mild, episodic wheezing to acute exacerbations with life-threatening dyspnea. The episodic and circadian nature of asthma’s symptoms are important considerations during the assessment of a patient. Wheezing, breathlessness, and cough occurring in an episodic fashion are the hallmarks of asthma. Because of this episodic nature, detailed pulmonary function tests cannot be performed frequently enough to provide much useful information. However, measures of the peak expiratory flow will be useful because they can be obtained easily at any time with small peak expiratory flow gauges that can be used at home. Drug therapy should be preceded by an attempt to control the patient’s exposure to environmental allergens and irritants.

Environmental risk factors in the development of asthma appear to be potentially preventable. It may be safe to assume that changes in lifestyle and exposure to allergens and sometimes dietary factors may be responsible in the development of asthma. However, diet as a risk factor is circumstantial. Asthma has a multifactorial etiology and several factors may play independent roles in its development. The evidence that allergens play a major role in asthma is undisputable. The levels of allergen exposure clearly influence the prevalence of airway hyperresponsiveness (AHR) in sensitized subjects. Sensitization to house dust-mite allergens and to mold spores in dry climate has been reported. The house dust-mite allergens are more important than cat and cockroach allergens in predisposing children to increased sensitization and morbidity.

The prevalence of asthma appears to be more common in some urbanized regions. Air pollution has been implicated in the increased prevalence of asthma. Studies have indicated that lifestyle factors associated with modern living conditions increase the symptoms. For example, children living in industrial regions may have more severe airway responsiveness than children living in rural regions. Exposure to passive smoking and its effects on lung function have been studied. Babies whose mothers smoke have increased hair cotinine and nicotine levels. Cotinine levels in young children are related to the number of smokers to whom the child is exposed. Other factors such as socioeconomic class and inadequate home ventilation may increase exposure and enhance its effects. Since it is well documented that allergens increase the severity of both AHR and morbidity, it is important that new approaches to avoid allergen exposure be explored. New methods may help reduce the incidence of asthma in all situations. Reduction of risk in even a minority of the children would lead to an important public health...
benefit. Some basic examples that improve health and markedly reduced allergen exposure include use of greater allergen-free furniture and homes, mattress covers, and improved ventilation.18-20

Allergen-specific immunotherapy has been used for many years in the treatment of asthma. Recent trials indicated that immunotherapy reduces asthma symptoms caused by house dust mites, cat dander, Alternaria and Cladosporium molds, and grass, birch tree, and ragweed pollen.21 Use of immunotherapy remains controversial because to my knowledge, no study has defined the amount of medication required that can significantly control the symptoms. Immunotherapy for at least 3 years is optimal in patients with seasonal allergic rhinitis.22 New forms of immunotherapy (sublingual and oral) have recently been tried in an attempt to improve on convenience, with beneficial results.23,24 Treatment of allergic rhinitis may result in an improvement in asthma symptoms. In the patient with allergic rhinitis, nasal corticosteroid therapy may prevent the seasonal increase in bronchial responsiveness to methacholine. Nasal corticosteroids may have a protective effect in patients with airway reactivity, perennial rhinitis, and asthma. Thus, rhinitis should be treated aggressively in all patients with allergic asthma.25,26

Other factors that have been implicated in the development of asthma are psychological factors. The prevalence and importance of psychogenic factors in asthma have been debated but evidence suggests that psychological stressors can lead to clinically significant deterioration in asthma control.27-29 It is known in certain asthma patients that psychological factors play an important role in the stability or instability of the disease and the patients’ ability to participate in cogent self-management planning. In a recent study, agoraphobia and panic disorder were more frequently seen in patients with asthma in outpatient clinics than in the general population.30 In that study, significant improvement was observed in patients who had autogenic therapy. Autogenic therapy is a psychophysiologic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Aerosol corticosteroids</td>
<td></td>
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</tr>
<tr>
<td>Beclomethasone</td>
<td>MDI, 43 µg per puff</td>
<td>8 puffs or 336 µg; reduce to 2 puffs twice per day when asthma is stable</td>
</tr>
<tr>
<td>Flunisolide</td>
<td></td>
<td>4 puffs or 1,000 µg; reduce to 2 puffs twice per day when asthma is stable</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td></td>
<td>8 puffs or 800 µg; reduce to 2 puffs twice per day when asthma is stable</td>
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*Theophylline can be used as an adjunct to step-two agents. Adapted with permission from Bone.2

Table 2—Agents to Consider in Step-Two Care*

PEF Measured Every Morning or More Frequently if Unstable

PEF ≥70% potential normal value, continue “maintenance regimen” of
(a) Inhaled β-sympathomimetic, as required
(b) Inhaled corticosteroid twice daily

PEF <70% potential normal value
(a) Double dose of inhaled corticosteroid for number of days required to achieve previous baseline
(b) Continue this increased dose for same number of days
(c) Return to previous dose of maintenance regimen

PEF <50% potential normal value
(a) Start oral prednisone therapy, 40 mg daily, and contact physician
(b) Continue this dose for the number of days required to achieve previous baseline
(c) Reduce oral prednisone therapy to 20 mg daily for same number of days
(d) Stop prednisone therapy

PEF <150-200 L/min
(a) Start oral prednisone therapy as above
(b) Contact physician urgently or, if he or she is unavailable
(c) Contact ambulance service or, if it is unavailable
(d) Go directly to hospital

*Adapted from Beasley et al.46
Table 4—Example of Management Plan*

<table>
<thead>
<tr>
<th>Potential Normal PEF (^1) 550 L/min</th>
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<tbody>
<tr>
<td>Routine treatment</td>
</tr>
<tr>
<td>Corticosteroid inhaler puff 2×day</td>
</tr>
<tr>
<td>Inhaled β-sympathomimetic inhaler as required</td>
</tr>
<tr>
<td>PEF &lt;400 L/min: Increase inhaled corticosteroid to 1 puff 4×day and inhaled β-sympathomimetic as required</td>
</tr>
<tr>
<td>PEF &lt;250 L/min: Prednisone, 40 mg/d until PEF &gt;500 L/min, then prednisone, 20 mg/d for same number of days</td>
</tr>
<tr>
<td>PEF &lt;150 L/min: Begin oral prednisone therapy as above and contact physician urgently or go to hospital emergency department</td>
</tr>
</tbody>
</table>

*Example of written management plan given to a male patient aged 39 years.

1Predicted PEF=540; best consistent PEF 550 L/min. Adapted from Beasley et al.46

Technique consisting of concentration on anatomic locations and physiologic processes in improving respiratory function.

TREATMENT

Treatment of asthma should be based on the severity of the disease. With the recognition of asthma as an inflammatory disease, the goal of the treatment should be to reduce bronchospasm and the inflammatory changes. Recently, the emphasis in the treatment has moved from treating the symptoms with bronchodilators such as β-agonists to prophylactic inhaled corticosteroid treatment. Step-care therapy has been designed with the goal of reducing or arresting the inflammatory processes underlying asthma.

STEP-CARE THERAPY

Step-care therapy is a systematic management approach for the control of asthma. Step-care therapy requires that the patient first be categorized as to the severity of disease (Table 1). Based on the severity of the disease, therapeutic approaches have been designed (step-one, step-two, or step-three therapy).4

Step-One Therapy

Step-one therapy is appropriate for patients who manifest mild symptoms on rare occasions. The lifestyle of these patients is not affected greatly by the disease. The clinical goal of step-one therapy is to provide prompt relief from the symptoms, which may be achieved usually with short-acting inhaled bronchodilators. Inhalers containing epinephrine are still available without prescription and provide moderate but relatively brief bronchodilation.

The adrenergic receptors important in the treatment of asthma are predominantly β-receptors. β-Receptors are subclassified as β₁-, β₂-, and β₃-receptors. Although other receptors are present in the lungs, bronchodilation is achieved mainly by β₂-receptors. These receptors are further divided based on the duration of action. These are short acting at 3- to 6-h duration of action, and those that are long acting have a duration of action of more than 12 h. β-Adrenergic agonists achieve their effects by binding to β₂-adrenergic receptors. These receptors belong to a large group of receptors whose effects are brought about by a cascade of events that include activation of a G-protein which, in turn, activates adenylyl cyclase to convert adenosine triphosphate to cyclic adenosine monophosphate. In the smooth muscles of the airways, cyclic adenosine monophosphate has the effect of relaxation, thus increasing the diameter of the airway. β₂-Agonists have nonbronchodilator effects in addition to bronchodilation. The nonbronchodilator effects include enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission, enhancement of vascular integrity, and inhibition of mediator release from mast cells, basophil, and also other cells. For relief of acute symptoms, and also for prevention of exercise-induced bronchospasm, more specific β₂-adrenergic agonists are preferred. They act rapidly (with a rapid peak effect) and locally with few side effects (Figs 1 and 2).

The limitations of short-acting β-agonists are (1) their inability to control the symptoms of nocturnal asthma and (2) their short duration of protection against exercise-induced bronchospasm. Both limitations are related to the short duration of action of these agents. These agents should be used as occasion requires for asthma symptoms. They should not be used unless there is a deterioration in peak flow or development of symptoms. Among the short-acting drugs that are currently available in the United States, there is little reason to choose one drug over the others.

Investigators continue to develop β-adrenergic agonists with improved activity. These forms are now more specific for the β₂-adrenergic receptor subtype found in the lung airways and have fewer cardiac effects. The adrenergic receptors themselves have also been the subject of intense interest, being almost ubiquitously expressed by human cells. The cloning of this gene has helped researchers to find new subtypes of the gene, while space-filling models have helped researchers to understand the finer points of receptor-ligand interactions.31
bronchoconstriction. The long-acting β₂-adrenergic agonists prevent nocturnal asthma and provide prolonged protection against exercise-induced bronchoconstriction. The long-acting β₂-adrenergic agonists should be administered only at regular, prescribed intervals. Short-acting β₂-agonists should be given instead of additional doses to relieve symptoms. Inhaled β₂-adrenergic agonists remain the most important class of bronchodilators currently available. When used appropriately, they provide safe and effective relief of symptoms of airflow obstruction.

An important hindrance to achieving the full benefits offered by β-agonists is the improper use of metered-dose inhalers (MDIs); as many as 50% of patients using MDIs do so incorrectly. These patients are not appropriately treated. Misuse often continues even after repeated rounds of instruction.33 The most significant problem seems to be coordinating the activation of the canister with an appropriate inhalation. Although the use of spacer devices is recommended, patients often do not carry them or do not use them. A patient’s MDI technique should be observed carefully by the physician who prescribes it. Other common problems with MDI use include failure to shake the canister before use, inadequate breath holding, and the failure to wait between puffs. Correct use of MDI is a skill taught through patient education.

To overcome this problem, an auto inhalation device has been introduced. This device is triggered by the patient’s inhalation rather than by hand actuation. Pulmonary function in patients receiving pirbuterol acetate via a MAXAIR Autoinhaler (3M Pharmaceuticals; St. Paul, Minn) and those patients using standard MDIs were compared. Both systems produced similar results in spirometry. This may be due to the two puffs of perbuterol regardless of the delivery system. Autoinhalers are as effective as correctly used MDIs and are a viable alternative for patients who have coordination problems with the standard MDI. Children whose peak inspiratory flow rate is less than 0.5 L/s may not be able to use the Autoinhaler correctly. Correct use of the Autoinhaler will depend on effectively educating patients.34,35

Anticholinergic agents, such as ipratropium bromide, are another form of drug that can be used in the treatment of mild, occasional asthma (step-one therapy), after inhaled β-agonists are used. Vagal tone releases acetylcholine at nerve endings on the airways, resulting in a tonic smooth muscle contraction. Although the numbers of acetylcholinergic receptors within the airway walls may vary considerably on an individual basis, treatment with anticholinergics can have a positive effect by inducing smooth muscle relaxation. Studies indicate that anticholinergics may be additive with β-agonists in providing relief to patients with asthma.36 Patients with nocturnal asthma may derive additional benefits from treatment with anticholinergics. Because of the increase in vagal tone that occurs during sleep, acetylcholine release at the airway smooth muscle may be implicated as a cause of nocturnal asthma, making anticholinergics an appropriate therapy in some patients. Inhaled ipratropium on waking has been shown to be effective in this condition.37

Theophylline and other methylxanthines improve pulmonary function, although the mechanisms by which they work have not been described adequately. Theophylline has a narrow therapeutic index and may be toxic at doses just above those effective for asthma treatment. Various guidelines for asthma management recommend the use of theophylline or aminophylline in cases that respond poorly to aerosol MDIs and for short-term exacerbations. Theophylline is regarded as a weak bronchodilator with a high toxicity potential and its use has been declining. Recently, however, theophylline’s properties as an anti-inflammatory agent and an immunomodulator have been emphasized. Although serious drug toxic reactions, including cognitive and behavioral side effects, have been reported, theophylline can add to and prolong the responses to β-agonists because it is also a weak anti-inflammatory agent. It should be considered for use in asthmatic patients who require oral corticosteroids.

It has been reported that low-dose therapy attenuates the late asthmatic inflammatory response to allergen through modulating an effect on lymphocytes, demonstrating the immunomodulatory role of theophylline. Long-acting theophylline in low doses, with a serum concentration of 5 to 10 mg/L, may have a significant effect in patients with unstable asthma. Theophylline, therefore, may have a more significant role in future guidelines for the management of asthma.5,6,38 Theophylline should be reserved for use as an adjunct in step-one or step-two therapy and if used, blood levels of the drug should be monitored frequently to prevent toxic reactions.
Step-Two Therapy

When a patient with mild asthma begins to use inhaled bronchodilators on a regular basis, it is a sign that the disease is worsening and that step-two therapy should be instituted (Table 2). Step-two therapy consists of daily medication with anti-inflammatory agents such as inhaled corticosteroids nedocromil or cromolyn plus bronchodilators (inhaled β₂-agonist as occasion requires, oral theophylline, oral β₂-agonist). The mainstay of this treatment level is an inhaled corticosteroid. Corticosteroids act by decreasing the inflammation that underlies hyperresponsivity and bronchospasm. The goal of their use is to manage the late-phase inflammatory response while minimizing treatment side effects. Inhaled corticosteroids have been shown to provide a protective effect against the deterioration in lung function seen with prolonged regular use of inhaled bronchodilator therapy alone.

Studies have shown that inhaled corticosteroids have little effect on exercise-induced bronchoconstriction (EIB), unless it is taken for several weeks. Although corticosteroids have the ability to attenuate EIB, inhaled corticosteroids will not replace inhaled β₂-agonists or cromolyn as the best prophylactic treatment for EIB. Inhaled corticosteroids have the ability to prevent or reduce airway inflammation and AHR. The anti-inflammatory effect of inhaled corticosteroids in the treatment of asthma has been demonstrated in several studies. Inhaled corticosteroids have been shown to decrease eosinophil number and density as well as improve epithelial quality and reduce inflammatory cell infiltrate.

There are several mechanisms involved in the inflammatory response that may be influenced by corticosteroid therapy. The two important areas that have been investigated are the decreased production of cysteinyl leukotrienes and interference with the action of proinflammatory cytokines. Cysteinyl leukotrienes are known to be involved in both early and late allergic asthmatic responses. Inhaled corticosteroid treatment attenuates both early and late responses; the increase in leukotriene E₄ excretion following allergen is not attenuated. It is known that corticosteroid treatment in vitro will inhibit phospholipase A₂ responsible for eicosanoid synthesis. The increase in leukotriene E₄ excretion following allergen challenge may reflect a whole-body increase in leukotriene production. Inhaled corticosteroids acting preferentially on the airway may thus decrease local leukotriene production without influencing urinary leukotriene E₄. Corticosteroids have been known to reduce airway levels of proinflammatory cytokines in patients with asthma.

A recently developed technique that should considerably improve treatment is the implementation of peak flowmeters. These small, easy-to-use gauges allow patients to measure their own peak expiratory flow rates at home. The difference between morning and evening peak flow rates provides an estimation of the airway reactivity. When the difference exceeds approximately 20% of the peak flow rate, additional therapy should be considered. Education, again, is the key word: properly instructed patients should be able to increase their own treatment dosage with inhaled corticosteroids at the first sign of an exacerbation.

A self-management plan in the treatment of adult asthma has been devised that is specifically designed to tackle the factors that contribute to death from asthma (Tables 3 and 4). This is a management regimen based on regular objective assessment of airflow obstruction in association with adequate inhaled corticosteroid treatment. This method was used in a study and has been shown to be effective for adults with chronic severe asthma. The management plan is incorporated with several different treatment guidelines. The combination of these guidelines may have contributed to the beneficial effect. The aim of this regimen is to start treatment with oral corticosteroids in sufficient dosage when required early in an attack, and to use the subsequent therapeutic response to determine the duration of the treatment. A combination of routine measurement of peak expiratory flow and a self-management plan appears to be effective in reducing symptoms of asthma and also improving lung function.

Cromolyn sodium and such related compounds as nedocromil sodium are another form of therapeutic agent appropriate for step-two therapy. Although their exact mechanisms of action are unknown, they appear to inhibit the release of inflammatory mediators by mast cells. By stopping the early-phase reaction in asthma, the tendency toward inflammation may be arrested before it starts. One of the most important problems with inhaled corticosteroids and cromolyn or nedocromil is the failure of patients to follow their treatment regimens. To the patient conditioned to the rapid and dramatic beneficial effects provided by the β₂-agonists, these drugs appear to be ineffective; additionally, they are relatively expensive. Failure to comply with the treatment regimen is common; patients must be instructed that these anti-inflammatory drugs alleviate the inflammatory response and that the benefits are long term and aimed at preventing exacerbations, rather than treating them. This approach also appears to inhibit both the late-phase reaction in asthma and the dramatic response usually obtained from challenges with allergens.

Longer acting inhaled β₂-adrenergic-agonist have overcome many of the shortcomings of previously available drugs (Fig 3). Currently, long-acting agonists with high specificity for the β₂-receptor are being developed, such as salmeterol xinafoate and formoterol. Salmeterol is now available for use in the United States,
while the use of formoterol is still being considered. The longer-acting β-agonists are more selective for the β2-adrenergic receptor and their activity persists for a longer period of time at the receptor site. Salmeterol is indicated for long-term, twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-term β2-agonists. It should not be used in patients when asthma can be managed with occasional use of short-acting β2-agonists.

Salmeterol should never be used more than twice daily. Increasing its use in an acute attack is inappropriate and may be dangerous. Salmeterol should not be used to treat acute asthma symptoms because it has a slower onset of action.46 Patients must be provided short-acting, inhaled β2-agonist for treatment of acute symptoms. Patients using salmeterol may feel well enough and may discontinue the anti-inflammatory therapy. This discontinuation could cause a serious exacerbation of asthma because salmeterol is not a substitute for oral or inhaled corticosteroid therapy. Its use may be beneficial in patients with nocturnal asthma and exercise-induced asthma as maintenance therapy.48-51

Although salmeterol is a major advance in the treatment of asthma based on the available data, salmeterol should be reserved for patients who are already receiving step-two anti-inflammatory therapy.48 Longer-acting agents improve sleep quality, morning peak-flow measurements, and nocturnal symptoms.49 In one 12-month trial of salmeterol vs albuterol, there was no deterioration with long-term administration. Salmeterol has also been shown to be effective for protection against EIB for up to and including 12 h in patients with mild to moderate asthma.50

**Step-Three Therapy**

Step-three therapy is reserved for patients whose asthma is not controlled by step-two treatment and consists of more aggressive forms of anti-inflammatory treatment, the mainstay of which is oral corticosteroids at doses high enough to stop the inflammation. The incidence of side effects, which can be serious with high-dose corticosteroids, is decreased by the use of agents with a short duration of action, such as prednisone. It is critical that treatment with these be instituted at the first indication of uncontrolled asthma. Too often in fatal asthma, anti-inflammatory drugs were administered too little and too late. Oral dosages of prednisone as high as 40 to 60 mg/d may be used for up to 2 weeks to counter serious exacerbations of asthma. Following such treatments, corticosteroid dosages should be tapered to maintenance levels of aerosol-administered drug. When a patient is particularly difficult to wean from corticosteroid therapy, long-term, alternate-day therapy may be a reasonable route. This method is less likely to result in such serious side effects of corticosteroid use as suppression of the adrenal gland, hypertension, and aseptic necrosis. Other, less serious effects of this medication may include fluid retention, mood changes, and GI upset.

From the point of view embraced by advocates of step-care treatment for asthma, the occurrence of an exacerbation requiring step-three therapy may be a failure of step-two therapy. Through appropriate use of the peak flowmeter, patients should be able to anticipate exacerbations and increase their dosage of corticosteroids accordingly. The goal of this form of patient-dispensed medication is to prevent the exacerbations of asthma that may require hospitalization and more radical forms of treatment.

The above ideas are consistent with the guidelines developed in 1991 by the National Asthma Education Program. The guidelines can be summarized in four key points: (1) pharmacologic therapy; (2) appropriate monitoring; (3) patient education; and (4) control of the environmental allergens and irritants that cause asthma. Recent studies have shown that inadequate patient education remains an impediment to appropriate treatment.53 One study has obtained promising results with the use of small-group instruction, which resulted in improved asthma control, even when compared with a program of individualized instruction. Not only did the patients derive support from within the group, but educators seem more at ease and were better able to understand the problems associated with treatment.54 To achieve adequate patient education, the patient-physician relationship must work well so that the patient can be taught how benefits may be derived from treatment. They must understand the long-term benefits as opposed to the short-term benefits of these treatments, a task that should be seen to by the physician. When patients understand their therapy, they are more likely to comply with the treatment and their asthma will be better managed.

**New Treatments**

Leukotrienes, which are products of 5-lipoxygenase pathway of arachidonic acid metabolism, are thought to be important mediators in the pathogenesis of asthma. Their biological activity produces changes that are similar to those seen in asthma. It was demonstrated that 5-lipoxygenase inhibitors or leukotriene receptor antagonists give good protection to patients undergoing acute allergen challenge in the laboratory. Recently, a new drug, Zileuton (Leutrol) was developed, which is an iron ligand inhibitor of 5-lipoxygenase.55,56
Several other new anti-inflammatory drugs have been developed. These drugs, which are currently being tested, may change the treatment strategy in the future. Although these drugs show promise in preclinical and early clinical trials, their efficacy and safety have not been determined. One of the new drugs that has reached phase 3 testing is Zafirlukast, a leukotriene-receptor blocker shows great promise as an anti-inflammatory agent. This drug binds specifically with a high degree of affinity to the leukotriene D and leukotriene E receptors, whereas the steroids block inflammation by inhibiting cytokine production. Zileuton acts by inhibiting the breakdown of arachidonic acid in the biosynthetic step to forming leukotrienes. Vasoactive intestinal peptide and antagonists to platelet activating factor are being developed for possible use in the treatment of asthma. Specific monoclonal or polyclonal antibodies, genetically modified or mass-produced endogenous molecules, and any other tools that can interfere with the pathogenesis of asthma and inflammation may become available in the future.

Management of asthma has become one of the most important challenges to the medical profession because of its increasing occurrence and the consequent unexplained mortality. Increasingly poor air quality has been expressed as one of the reasons for the rise in mortality. The multifactorial nature of the disease explains why some patients respond to some treatments while others do not. The essential part of the diagnosis should be the determination of patient's response to various treatments. The future looks promising as several new drugs with various anti-inflammatory actions may become available for use in the treatment of asthma.

REFERENCES
1 Reed CE. New therapeutic approaches in asthma. J Allergy Clin Immunol 1986; 77:537-43
3 Bone RC. Step care for asthma. JAMA 1988; 260:543
4 National Heart, Lung, and Blood Institute. National asthma education program: expert panel on the management of asthma: guidelines for the diagnosis and management of asthma. Dept of Health and Human Services publication (NIH) 1991-3042
7 Holgate ST. The role of mediators and inflammation in asthma. J Respir Dis 1987; 8:20-37
9 Hetzel MR, Clark TJH. Comparison of normal and asthmatic circadian rhythms in peak inspiratory flow rate. Thorax 1990; 152:511-17
11 Seaton A, Godden DJ, Brown K. Increases in asthma: a more toxic environment or a more susceptible population? Thorax 1994; 49:171-74
14 Magnussen H, Jorres R. Effect of air pollution on the prevalence of asthma and allergy: lessons from the German reunification. Thorax 1993; 48:879-81
19 Tovey E. House dust control measures: are they worthwhile? Mod Med Aust 1993; 8:118-27
20 Warner JA. Creating optimal home conditions for the dust-mite. Clin Exp Allergy 1994; 24:207-09
22 Mosbech H, Oesterballe O. Does the effect of immunotherapy last after termination of treatment? Allergy 1988; 43:523-29
29 Davis D. Asthma and the psyche [editorial]. Thorax 1993; 48:511
34 Henriksen JM. Effect of inhalation of corticosteroids on exercise-induced asthma: randomized double blind crossover study of
37 Morrison JFJ, Pearson SB, Dean HG. Parasympathetic nervous system in nocturnal asthma. BMJ 1988; 296:1427-29
40 Pederson S, Frost L, Armfield T. Errors in inhalation technique and efficacy in inhaler use in asthmatic children. Allergy 1986; 41:118-24
43 Green SA, Holt BD, Liggett SB. Beta2 and beta-adrenergic receptors display subtype-selective coupling to Gs. Mol Pharmacol 1992; 41:889-93
45 Bone RC. A word of caution regarding a new long-acting bronchodilator. JAMA 1994; 271:1448
47 Bone RC. Another word of caution regarding a new long-acting bronchodilator. JAMA 1995; 273:967-68
48 Douglas NJ. Nocturnal asthma. Thorax 1993; 48:100-02
49 Kemp JP, Bierman CW, Cocchettro DM. Dose response study of inhaled salmeterol in asthmatic patients with 24-hour spirometry and holter monitoring. Ann Allergy 1993; 70:316-22
60 Ford-Hutchinson A. Leukotriene antagonists and inhibitors as modulators of IgE-mediated reactions. Springer Semin Immunopathol 1993; 15:37-50