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Learning Objectives

1. Assess the benefits of combination therapy in treating chronic asthma for pediatric and adult patients.
2. Given patient-specific information, formulate a clinical plan of appropriate pharmacological therapy, monitoring plans, and patient education for adults with chronic asthma.
3. Given patient-specific information, formulate a clinical plan of appropriate pharmacological therapy, monitoring plans, and patient education for pediatric patients with chronic asthma.
4. Given patient-specific information, formulate a clinical plan of appropriate pharmacological therapy, monitoring plans, and patient education for pregnant patients with chronic and acute asthma.
5. Given patient-specific information, formulate a clinical plan of appropriate pharmacological therapy and monitoring for acute asthma.
6. Distinguish between the different types of monitoring plans—including written action plans, peak flow-based action plans, and symptom-based action plans—and explain their use.

Introduction

Asthma is one of the most common chronic conditions in the United States, affecting more than 20 million Americans. In fact, asthma is the most common chronic disease in children, resulting in more than 10 million school days missed per year. The impact of this disease on society, health care costs, and lost productivity at work or in school is immense. Knowledge of the pathophysiology of asthma is expanding, but is still incomplete, and the number of Americans suffering from asthma continues to rise.

To help combat this growing health care problem, in 1989 the National Asthma Education and Prevention Program (NAEPP) was formed by the National Heart, Lung, and Blood Institute to improve the quality of life of patients with asthma and to reduce asthma-related illness and death. Since its inception, the NAEPP has convened an expert panel to periodically review literature and develop and revise guidelines to reflect the most recent scientific advances to treat asthma. The most recent update, NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002, is a supplement to the most current fully updated guidelines published in 1997. Previous versions of the guidelines were completely rewritten to incorporate the latest scientific findings. The Update on Selected Topics addresses specific questions related to drug use and safety, monitoring of asthma, and prevention of asthma.

The majority of the topics reviewed in the 2002 update involve the treatment and management of pediatric patients with asthma. The Childhood Asthma Management Program study was a well-designed, long-term study conducted in pediatric patients and was the primary resource for the expert panel's recommendations. Although it was the longest and largest study conducted regarding treatment of asthma in children, the Childhood Asthma Management Program study included patients with mild to moderate asthma and did not answer questions about children with severe asthma. The Childhood Asthma Management Program study report was thoroughly reviewed in the Update on Selected Topics 2002. Reports of other studies were also reviewed for the update but the studies were smaller and of shorter duration. This chapter addresses the issues discussed in the Update on Selected Topics 2002.

In addition to the NAEPP guidelines for treating asthma, the Global Initiative for Asthma (GINA) guidelines are also available. Initiated in 1993, GINA was formed in collaboration with the National Heart, Lung, and Blood

Abbreviations in this Chapter

BHR	Bronchial hyperresponsiveness
FEV ₁	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
HFA	Hydrofluoroalkane
IgE	Immunoglobulin E
NAEPP	National Asthma Education and Prevention Program

Institute, the National Institutes of Health, and the World Health Organization. Similar to the NAEPP asthma guidelines, GINA has a scientific committee that evaluates scientific literature and makes recommendations on the care of patients with asthma. The GINA guidelines are updated yearly and are accessible through a Web site (www.ginasthma.com). Although the GINA guidelines are similar in structure to the NAEPP guidelines, some differences are discussed in this chapter.

Pathophysiology

Definition

The current definition of asthma states that it is a chronic inflammatory disease in the airways that involves multiple cells and mediators. These include eosinophils, mast cells, T-lymphocytes and neutrophils. Patients respond to this inflammatory process with symptoms of daytime and nocturnal cough, wheezing, and breathlessness. These episodes either reverse on their own or with drugs. The inflammatory response also results in the patient having bronchial hyperresponsiveness (BHR), and airway remodeling.

Etiology

Although the etiology of asthma has not been identified, it is thought that there is an interaction between a patient's genetic susceptibility to develop asthma and environmental exposures, both of which have been under intense investigation. Genetic screenings identified susceptibility loci, which may be involved in the pathogenesis of asthma. Phenotypes that have been identified with genetic loci include mucus production, regulation of total serum immunoglobulin E (IgE) levels, and BHR. Although a plethora of information is available regarding genes potentially associated with asthma, the clinical significance of these data is still lacking. Studies that identify genotypes predictive of asthma phenotypes are necessary for genetic information to become meaningful in diagnosing and treating of asthma.

Clinical Characteristics

Due to the heterogeneity of asthma, patients may present to their health care practitioners in a variety of ways, leading to difficulties in establishing a diagnosis and selecting appropriate treatment. Clinical features can include coughing, wheezing, chest tightness, and breathlessness with symptoms from mild to life-threatening. The symptoms of asthma, along with BHR, are caused by airway inflammation. Studies show that even patients with mild asthma have ongoing inflammation in their airways. Diagnosing the disease can be difficult because the nonspecific nature of asthma symptoms can be attributed to many different disease states, including cystic fibrosis, vocal cord dysfunction, and congestive heart failure.

Perimenstrual

It appears that a subset of females with asthma experience an increase of their asthma symptoms during the perimenstrual or menstrual phase of their cycles. Studies indicate that up to 40% of women have reported this experience. Perimenstrual asthma seems likely to be associated with fluctuations in hormone levels; however, this has not been consistently shown in studies. Even though perimenstrual asthma has been associated with an increase in asthma symptoms and a decrease in peak expiratory flow, changes in other lung function tests and BHR have been inconsistent. A recent study showed that significantly more near-fatal asthma exacerbations occurred on the first day of menses compared with other days. Clearly, this area requires more study.

Diagnosis and Assessment

The gold standard for diagnosing asthma is spirometry before and after administration of a short-acting inhaled β_2 -agonist with an improvement in forced expiratory volume in one second (FEV₁) of 12% or greater over baseline. The NAEPP and GINA guidelines both have criteria for determining the severity of a patient's asthma and classify asthma as intermittent, or mild, moderate or severe persistent. The GINA guidelines also include a patient's current drug regimen and his or her response to therapy (Table 1-1). This classification system takes into consideration the patient's nocturnal awakenings due to asthma, daytime symptoms, and spirometry and circadian variation in lung function. Classification is based on the patient's most severe category, and treatment is determined by the classification.

Despite these guidelines, evidence suggests a poor correlation between the clinical classification of asthma severity and a patient's perceptions of his or her asthma severity. Experts have determined that although most patients with asthma fall into the mild intermittent and mild persistent categories, patients with asthma tend to feel that

Vrieze A, Postma DS, Kerstjens HA. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* 2003;112:271–82.

Table 1-1. Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment

Patient Symptoms and Lung Function on Current Therapy	Current Treatment Step		
	Step 1: Intermittent	Step 2: Mild Persistent	Step 3: Moderate Persistent
	Level of Severity		
Step 1: Intermittent Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month Normal lung function between episodes	Intermittent	Mild Persistent	Moderate Persistent
Step 2: Mild Persistent Symptoms more than once a week but less than once a day Nocturnal symptoms more than twice a month but less than once a week Normal lung function between episodes	Mild Persistent	Moderate Persistent	Severe Persistent
Step 3: Moderate Persistent Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms at least once a week 60% < FEV ₁ < 80% predicted or 60% < PEF < 80% of personal best	Moderate Persistent	Severe Persistent	Severe Persistent
Step 4: Severe Persistent Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms FEV ₁ ≤ 60% predicted or PEF ≤ 60% of personal best	Severe Persistent	Severe Persistent	Severe Persistent

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

National Institutes of Health, National Heart, Lung, and Blood Institute. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention Revised (2002). NHLBI/WHO Workshop Report. NIH Publication No. 02-3659. Bethesda, MD: United States Department of Health and Human Services, 2002.

they have more severe disease. This lack of agreement can lead to misunderstanding and mistreatment of asthma.

Epidemiology

In 2001, it was estimated that almost 20.3 million people in the United States had asthma, which corresponded to an overall rate of 73.4 per 1000 people. The prevalence rate was highest in children ages 5–17 years of age (98.1 per 1000) and was inversely related to age. These data indicate that the prevalence rate in females was 30% greater than in males, but in children younger than 18, the prevalence was 30% higher in males. From 1997 to 1999 there was a decline or a plateau of asthma prevalence, but findings for 2000 and 2001 reflected an incline, suggesting once again that asthma is on the rise.

Although the overall asthma prevalence appears to be increasing, mortality and hospital discharges are declining. The number of deaths due to asthma was about 4% higher in 1999 when compared with data from 2000. Annually, asthma is responsible for about 14.5 million lost workdays for adults and 14 million lost school days for children.

Prognosis and Natural History

The overall prognosis for patients with asthma is good. Even though there is not a cure for asthma, symptom control with appropriate treatment is certainly attainable for the majority of patients.

Several long-term studies are being conducted to help define the natural history of asthma. The Tucson Children's Respiratory Study began in 1980 and has been following 1246 subjects from birth. Through this work, the investigators defined three types of children with wheezing: 1) the transient wheezers who have a few wheezing episodes during the first 2–3 years of life and who do not wheeze after age 3; 2) the nonatopic wheezers who wheeze early in life, experience a lower respiratory tract infection early in life, and wheeze beyond their third birthday; and 3) atopic wheezers who are further classified as early atopic wheezers (who experience symptoms during the first 3 years of life) and as late atopic wheezers. Irrespective of subgroup, all atopic wheezers were sensitized to aeroallergens by age 6. Investigators developed the "Asthma Predictive Index" to identify children who will develop into atopic wheezers.

Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661–75.

Children with a positive index had wheezing during the previous year and 1 of 2 major criteria or 2 minor criteria. The major criteria are physician-diagnosed atopic dermatitis or parental asthma. The minor criteria are peripheral blood eosinophilia, wheezing apart from colds, or physician-diagnosed allergic rhinitis. In children who had a positive index, more than 75% had symptoms consistent with asthma at least once between the ages of 6 and 13; however, 68% of children with a negative index did not have symptoms consistent with asthma.

The Update on Selected Topics 2002 addressed the question of whether early intervention with long-term control therapy could prevent the progression of asthma in terms of declining lung function and symptom severity. The expert panel concluded that not enough evidence existed to answer the question. It stated, however, that a decline in lung function over time in children ages 5–12 with mild or moderate persistent asthma has not been supported in clinical trials regardless of treatment. Because a decline in asthma control (measured by BHR, symptoms, and lung function) has been seen on discontinuation of long-term control medication, it is implied that treatment can control but not modify the disease. However, observational studies in different age groups indicate that a rapid decline in lung function can occur in very young children (younger than 3 years old) and adults (20 and older) regardless of treatment. Research suggests that the variability in the progression of asthma is likely dependent on age rather than symptoms. Studies to determine if treatment can prevent this decline in lung function in these age groups have yet to be completed.

Therapeutic Goals and Outcomes

The goals of asthma therapy are clearly outlined by the NAEPP and GINA guidelines and include the following: prevent chronic symptoms and recurrent exacerbations; minimize emergency department visits and hospitalizations; avoid adverse effects of drugs while receiving optimal therapy; maintain normal pulmonary function and normal levels of activity; and meet patients' and families' expectations of therapy. In addition, the health care provider should ask patients how asthma is impeding their life (e.g., unable to participate in sports) and incorporate their responses into patient-specific treatment goals. Pharmacists can address these issues when patients refill their drugs or are discharged from the hospital.

Although therapy goals for asthma management have been identified for several years, there is increasing concern that these goals, specifically symptom control and maintaining normal daily activities, are not being achieved in the majority of patients. A recent study using Asthma Insights and Reality surveys looked at a cross-section of households in 29 countries in North America, Europe and

Asia. The objective was to assess international variation in asthma control, severity, and management. The survey collected data on access to medical care, health care use, missed work or school days, disease management practices, and patient perception of asthma control and severity. More than 10,000 surveys were completed, and despite some variations between countries (e.g., cultural differences and urbanization), the study showed that the goals of asthma therapy were not being met. The number of patients who experienced symptoms during the day ranged from 74% in central and eastern Europe to 51% in the Asia-Pacific region and Japan; 61% of patients in the United States reported daytime symptoms. In central and eastern Europe, 68% of patients experienced limitations in their activities. In the United States 36% of patients had their activities limited, whereas Japan had the lowest number (17%). The other therapy goals had similar findings. This study also found that a large percentage of patients overestimated control of their asthma. Overestimating control can cause patients not to seek further medical treatment and can also indicate that medical personnel are not adequately communicating to patients what they can expect from asthma therapy.

A prospective study was conducted to address the concern that the NAEPP goals of asthma control are not attainable. This well-designed, 1-year study compared two different long-term control therapies (monotherapy with an inhaled corticosteroid vs. the combination of an inhaled corticosteroid and a long-acting inhaled β_2 -agonist) and their ability to achieve the NAEPP and GINA recommended goals of therapy. Patients were assessed every 3–4 months for achieving the NAEPP and GINA goals of therapy, with the long-term control therapy increased if the goals were not being met. In contrast with the survey results, this study found that at least 50% of patients were able to achieve asthma control as defined by the guidelines with patients receiving combination therapy doing significantly better than those receiving monotherapy. This study indicates that asthma control is achievable; however, it can take several months to achieve. Health care providers must be persistent with patient follow-up, adherence, and communication of therapy expectations. These issues may not have been captured by the surveys and are not always achieved in a "real life" setting.

Quality Patient Care

Pharmacotherapy Update

Long-acting Inhaled β_2 -agonists

Salmeterol

Before 2003, salmeterol was available in a metered-dose inhaler and in a dry powder inhaler. During that year, the metered-dose inhaler was discontinued, and salmeterol is currently available only as a dry powder inhaler. This change has affected the treatment of asthma in patients for whom a long-acting inhaled β_2 -agonist is recommended, but

Rabe KF, Adachi M, Lai CK, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40–7.

Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control Study. *Am J Respir Crit Care Med* 2004;170:836–44.

are not able to use a dry powder inhaler, such as young children. Without the availability of a long-acting inhaled β_2 -agonist in a metered-dose inhaler formulation, clinicians have been forced to treat patients with higher doses of inhaled corticosteroids or with add-on therapies that have not been as effective as a long-acting inhaled β_2 -agonist.

In August 2003, the Food and Drug Administration required new safety information and warnings to be added to the labeling for salmeterol and drug products containing salmeterol. A boxed warning about a small but significant increased risk of life-threatening asthma attacks or asthma-related deaths was added to the new labeling. This warning was based on events experienced by patients taking salmeterol in a United States safety study, the Salmeterol Multicenter Asthma Research Trial. Results showed an overall numerical but not statistically significant increase in the risk of death or life-threatening asthma. The subanalysis indicated that this increased risk reflected a difference in response in African Americans who made up 17% of the population and was found predominantly in patients who were receiving only salmeterol and not inhaled corticosteroids. This study emphasizes that salmeterol should be used in conjunction with an inhaled corticosteroid in patients with asthma.

Formoterol

A second long-acting inhaled β_2 -agonist, formoterol fumarate, gained Food and Drug Administration labeling approval in 2001. It is approved for use in patients 5 years of age and older. Although similar to salmeterol in duration of action, formoterol has a faster onset of action (less than 5 minutes) than salmeterol (20 minutes). Formoterol is available in a capsule, which contains dry powder to be used with the Aerolizer inhaler. Currently, Phase III studies are in progress investigating the use of formoterol in another dry

powder inhaler, the Certihaler. Phase III studies are also examining the combination of formoterol with an inhaled corticosteroid (budesonide) in a hydrofluoroalkane (HFA) metered-dose inhaler.

Inhaled Corticosteroids

The Update on Selected Topics 2002 includes a new comparative daily dosage chart for inhaled corticosteroids for both adults and children (Table 1-2). This chart includes new formulations of inhaled corticosteroids, such as beclomethasone with a HFA propellant and budesonide suspension for nebulization. The chart also reflects changes in the comparative doses for budesonide in the dry powder inhaler formulation.

Leukotriene Receptor Antagonists

Montelukast Age Indication

Montelukast is now indicated for managing asthma in adult and pediatric patients as young as 12 months old. A new formulation as oral granules (4 mg of montelukast) is recommended for the pediatric population and can be administered either directly into the child's mouth or mixed with soft foods. Based on stability studies, it is recommended that the granules be mixed in carrots, applesauce, ice cream, or rice and served cold or at room temperature.

Intravenous Montelukast

A preliminary investigation of intravenous montelukast in adults with acute asthma reported a statistically significant but small improvement in FEV₁ (14.8%) that was maintained for 2 hours. The clinical significance of a 14.8% increase from a baseline FEV₁ of 1.6 liters remains unclear and will require more studies to evaluate the benefit of intravenous montelukast in the management of acute asthma.

Table 1-2. Estimate Comparative Daily Dosages for Inhaled Corticosteroids

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Adult	Child ^a	Adult	Child ^a	Adult	Child ^a
Beclomethasone CFC 42 or 84 mcg/puff	168–504 mcg	84–336 mcg	504–840 mcg	336–672 mcg	> 840 mcg	> 672 mcg
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	80–160 mcg	240–480 mcg	160–320 mcg	> 480 mcg	> 320 mcg
Budesonide DPI 200 mcg/inhalation	200–600 mcg	200–400 mcg	600–1200 mcg	400–800 mcg	> 1200 mcg	> 800 mcg
Inhalation suspension for nebulization (child dose)		0.5 mg		1.0 mg		2.0 mg
Flunisolide 250 mcg/puff	500–1000 mcg	500–750 mcg	1000–2000 mcg	1000–1250 mcg	> 2000 mcg	> 1250 mcg
Fluticasone MDI: 44, 110, or 220 mcg/puff	88–264 mcg	88–176 mcg	264–660 mcg	176–440 mcg	> 660 mcg	> 440 mcg
DPI: 50, 100, or 250 mcg/ inhalation	100–300 mcg	100–200 mcg	300–600 mcg	200–400 mcg	> 600 mcg	> 400 mcg
Triamcinolone acetonide 100 mcg/puff	400–1000 mcg	400–800 mcg	1000–2000 mcg	800–1200 mcg	> 2000 mcg	> 1200 mcg

^aChildren ≤ 12 years of age.

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler.

National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. NIH Publication 02-5074. Bethesda, MD: United States Department of Health and Human Services, 2003.

Zafirlukast Age Indication

Zafirlukast is now indicated for adults and pediatric patients 5 years and older. The recommended dose for children ages 5–15 is 10 mg 2 times/day compared with 20 mg 2 times/day for patients ages 12 and older.

Anti-immunoglobulin E Therapy

Omalizumab

Omalizumab is a recombinant humanized monoclonal antibody against IgE. Omalizumab is approved and indicated for adults and children ages 12 and older with moderate to persistent asthma. It is indicated for patients with asthma who have a positive skin test or in vitro reactivity to perennial aeroallergens and who have not been adequately controlled with inhaled corticosteroids. The drug dose, administered subcutaneously, is based on the patient's weight and initial serum total IgE level. The dose of the drug determines the dosing frequency, which is every 2–4 weeks. During therapy, IgE levels are not to be monitored. A review of omalizumab in the Cochrane Database concluded that omalizumab was superior to placebo in reducing the dose of inhaled corticosteroids by about 50%. Of interest, though, patients who were treated with placebo were also able to reduce their dose of inhaled corticosteroids. As a result, the clinical effect of omalizumab was small compared with placebo. However, omalizumab decreased asthma exacerbations when used as adjunctive therapy, and the effect was sustained when the dose of inhaled corticosteroid was decreased. Lung function parameters did not improve significantly with omalizumab compared with the baseline or placebo group. The cost-effectiveness of omalizumab as well as its long-term efficacy remains to be determined.

Short-acting Inhaled β_2 -agonist

The potential for detrimental effects on asthma control when using a scheduled short-acting inhaled β_2 -agonist has been controversial for more than a decade. Although placebo-controlled trials show that using regularly scheduled albuterol does not have detrimental effects on asthma control, several studies suggest differing responses based on the genotype at codon 16 of the β_2 -adrenergic receptor and on whether albuterol is given as two inhalations 4 times/day versus as-needed only. Retrospective studies indicate that patients who were homozygous for arginine at the 16th position of the β_2 -adrenergic receptor experienced decreased airflow and asthma control when they used albuterol on a scheduled basis. A recently published, prospective trial stratified patients based on genotype and found a decrease in the primary end point, morning peak expiratory flow, in the group homozygous for arginine after 16 weeks of daily albuterol use (two puffs 4 times/day) compared with when they received placebo. Although the results of this study are certainly intriguing, it is premature to base the care of patients with asthma on their genotype at this point. Nevertheless, it does raise the need to confirm

these findings and also look at the effects of long-acting inhaled β_2 -agonists.

Levalbuterol

Levalbuterol is the therapeutically active R-isomer of racemic albuterol and received an approved label indication from the Food and Drug Administration in 1999. Although the use of a single isomer agent has theoretical advantages over the use of a racemic agent, this has not been demonstrated for albuterol. It has been suggested that levalbuterol is more potent than racemic albuterol; however, studies have not supported this hypothesis. In fact, none of the studies demonstrated a dose-response relationship. Furthermore, well-designed studies completed in adult and pediatric patients with stable asthma and acute asthma exacerbations have not distinguished a difference between levalbuterol and albuterol. Considering that the cost of levalbuterol can be up to five times more than albuterol, advantages of using levalbuterol are questionable.

Allergen Immunotherapy

The use of allergen immunotherapy in treating asthma has long been a topic of debate. A Cochrane review of this practice included 75 trials. The trials included immunotherapy given for house mite, pollen, animal dander, *Cladosporium* mold, latex, and multiple allergens. This review concluded that immunotherapy reduced asthma symptoms and use of asthma drugs. The review also stated that although BHR improved, there were inconsistent findings on the results of lung function tests. Using immunotherapy may have some benefit for patients, but it is necessary for the health care provider to weigh the risks associated with immunotherapy, including anaphylaxis and cost.

Other Treatments

Studies have estimated that 40%–50% of patients with asthma have tried some form of complementary or alternative therapy, such as massage, herbal remedies, acupuncture, and nutrient supplementation. Completed Cochrane reviews have looked at different complementary or alternative therapies used in treating asthma. Reviews on the use of acupuncture, homeopathy, dietary salt reduction or exclusion, and vitamin C supplementation concluded that not enough evidence existed to recommend their use in treating chronic asthma. A review on using selenium supplementation concluded that there was some evidence suggesting that patients receiving the supplement experienced some improvement in “clinical evaluation;” however, improvements in objective measurements (lung function and BHR) did not exist, limiting the conclusions. One study compared patient-reported food intake to asthma outcomes. Patients were asked to complete a validated, self-administered questionnaire on their food intake for the previous month. The only association found was between

Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2004;(3):CD003559.

Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004;364:1505–12.

asthma severity and genistein, a soy isoflavone. The FEV₁ in patients who consumed genistein was 82.1% of predicted while the FEV₁ in patients who did not consume genistein was 76.2%. The results of this study cannot assume a causal relationship, and randomized, prospective studies need to be completed to validate these findings.

Treatment Plans

Chronic Therapy

The Update on Selected Topics 2002 addressed several issues regarding chronic therapy for asthma and made new recommendations for the chronic treatment of children younger than 5 years old (Figure 1-1) and children older than age 5 and adults (Figure 1-2).

One of the questions addressed by the expert panel was whether the use of chronic inhaled corticosteroids improved the long-term outcomes in children with mild or moderate persistent asthma when compared with other drugs. The expert panel found that there was sufficient evidence to support the chronic use of inhaled corticosteroids in children. Asthma control, measured by spirometry, BHR, symptoms scores, oral steroid use, urgent care visits, and hospitalizations was significantly better in children who received inhaled corticosteroids compared with as-needed short-acting inhaled β_2 -agonists, long-acting β_2 -agonists, theophylline, nedocromil, cromolyn, or leukotriene modifiers. This finding resulted in a change in the treatment guidelines for children younger than age 5. The Update on Selected Topics 2002 now recommends that the use of inhaled corticosteroids in this population is the preferred therapy and labels the other treatments “alternative treatments.” More recently, a double-blind trial found that adults with stable, mild persistent asthma may be adequately controlled with as-needed oral or inhaled corticosteroids instead of daily inhaled corticosteroids. However, this result is in contrast to previously published trials in patients with mild persistent asthma, so additional data are required before conclusions can be made.

Although the NAEPP guidelines recommends using inhaled corticosteroids as first-line therapy for treating asthma, health care providers are becoming increasingly aware of the variability in patient response to long-term control therapy. The National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network investigated this question by conducting a well-designed clinical trial examining the variability in patient response to two treatments, fluticasone and montelukast. The investigation also identified patient clinical features that resulted in a more favorable response. Seventeen percent of patients responded to both inhaled corticosteroids and leukotriene receptor antagonist, 23% responded to the inhaled corticosteroid only, 5% responded to the leukotriene receptor antagonist only, and 55% responded to neither treatment. Compared with subjects not responding to either drug, patients who responded only to the inhaled corticosteroid had higher levels of exhaled nitric

oxide, total eosinophils counts, serum IgE, and serum eosinophil cationic protein levels. The inhaled corticosteroid responders also had increased BHR and lower pulmonary function. The leukotriene receptor antagonist-only responders were younger and had asthma for a shorter length of time. Although identifying appropriate therapy based on patient-specific phenotypic characteristics is an exciting concept, limitations of the study, including the narrow definition of a responder and the short duration of the treatment (8 weeks), need to be addressed in future research.

Another issue addressed by the expert panel was the long-term adverse effects of inhaled corticosteroids in children. The Childhood Asthma Management Program study addressed this subject in a study of children with asthma who were followed for up to 6 years (average 4.3 years). Results showed that using inhaled corticosteroids did not have effects on any of the predefined outcomes, including bone mineral density, ocular toxicity, suppression of the hypothalamic-pituitary-adrenal axis, and vertical growth. This study showed that low to medium doses of inhaled corticosteroids decreased the children’s growth velocity during the first year of use, but that this decrease was not sustained during subsequent years of inhaled corticosteroid use. However, after an average of 4.3 years of follow up, the children had not experienced catch up growth. Cohort studies following children receiving inhaled corticosteroids for more than 10 years demonstrated no difference in the final height of children with asthma compared with healthy normal children and children with asthma who did not receive steroids. As a result, the expert panel concluded that low to medium doses of inhaled corticosteroids do not have clinically significant effects on the outcomes measured, and the potential risks are well balanced considering the effectiveness of inhaled corticosteroids.

Although the Update on Selected Topics 2002 recommends inhaled corticosteroids as the preferred therapy for treating all levels of persistent asthma, it also addressed the issue of whether adding another long-term control drug (long-acting inhaled β_2 -agonist, leukotriene receptor antagonist, or theophylline) could improve outcomes for patients with asthma. The most consistent evidence from well-designed clinical trials in adults indicate that the addition of a long-acting inhaled β_2 -agonist improves lung function and decreases the use of as-needed inhaled short-acting β_2 -agonists in patients not adequately controlled on low to medium doses of inhaled corticosteroids. It is theorized that the improvement in asthma control seen with the combination of inhaled corticosteroids and a long-acting inhaled β_2 -agonist is a result of their complementary mechanisms of action. At low doses, inhaled corticosteroids suppress chronic inflammation and decrease BHR in the majority of patients. Long-acting inhaled β_2 -agonists may increase nuclear

Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519–28.

Szeffler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233–42.



Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required to Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	Daily Medications
Step 4 Severe Persistent	Continual Frequent	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – High-dose inhaled corticosteroids AND – Long-acting inhaled beta₂-agonists AND, if needed, <ul style="list-style-type: none"> – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	<ul style="list-style-type: none"> ■ Preferred treatments: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids and long-acting inhaled beta₂-agonists OR – Medium-dose inhaled corticosteroids ■ Alternative treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline. <p>.....</p> <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Medium-dose inhaled corticosteroids and long-acting beta₂-agonists. ■ Alternative treatment <ul style="list-style-type: none"> – Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids (with nebulizer or MDI with holding chamber with or without face mask or DPI). ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	<ul style="list-style-type: none"> ■ No daily medication needed.
Quick Relief All Patients <ul style="list-style-type: none"> ■ Bronchodilator as needed for symptoms. Intensity of treatment will depend upon severity of exacerbation. <ul style="list-style-type: none"> – Preferred treatment: Short-acting inhaled beta₂-agonists by nebulizer or face mask and space/holding chamber – Alternative treatment: Oral beta₂-agonist ■ With viral respiratory infection <ul style="list-style-type: none"> – Bronchodilator q 4–6 hours up to 24 hours (longer with physician consult); in general, repeat no more than once every 6 weeks – Consider systemic corticosteroid if exacerbation is severe or patient has history of previous severe exacerbations ■ Use of short-acting beta₂-agonists > 2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy. 		
 Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible  Step up If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.		Note <ul style="list-style-type: none"> ❑ The stepwise approach is intended to assist, not replace, the clinical decisionmaking required to meet individual patient needs. ❑ Classify severity: assign patient to most severe step in which any feature occurs. ❑ There are very few studies on asthma therapy for infants. ❑ Gain control as quickly as possible (a course of short systemic corticosteroids may be required); then step down to the least medication necessary to maintain control. ❑ Minimize use of short-acting inhaled beta₂-agonists. Overreliance on short-acting inhaled beta₂-agonists (e.g., use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy. ❑ Provide parent education on asthma management and controlling environment factors that make asthma worse (e.g., allergies and irritants). ❑ Consultation with an asthma specialist is recommended for patients with moderate or severe persistent asthma. Consider consultation for patients with mild persistent asthma.
Goals of Therapy: Asthma Control <ul style="list-style-type: none"> ■ Minimal or no chronic symptoms day or night ■ Minimal or no exacerbations ■ No limitations on activities; no school/parent's work missed ■ Minimal use of short-acting inhaled beta₂-agonist ■ Minimal or no adverse effects from medications 		

Figure 1-1. Stepwise approach for managing infants and young children (5 years of age and younger) with acute or chronic asthma.

DPI = dry powder inhaler; MDI = metered-dose inhaler.

National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. NIH Publication 02-5074. Bethesda, MD: United States Department of Health and Human Services, 2003.

Classify Severity: Clinical Features Before Treatment or Adequate Control			Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	PEF or FEV ₁ PEF Variability	Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – High-dose inhaled corticosteroids AND – Long-acting inhaled beta₂-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	> 60% – < 80% > 30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-to-medium dose inhaled corticosteroids and long-acting inhaled beta₂-agonists. ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled beta₂-agonists. ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	≥ 80% 20–30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids. ■ Alternative treatment (listed alphabetically): cromolyn, leukotriene modifier, nedocromil, OR sustained-release theophylline to serum concentration of 5–15 mcg/mL.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	≥ 80% < 20%	<ul style="list-style-type: none"> ■ No daily medication needed. ■ Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

Quick Relief All Patients	<ul style="list-style-type: none"> ■ Short-acting bronchodilator: 2–4 puffs short-acting inhaled beta₂-agonists as needed for symptoms. ■ Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed. ■ Use of short-acting beta₂-agonists >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.
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<div>  Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible. </div> <div>  Step up If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control. </div>	Goals of Therapy: Asthma Control <ul style="list-style-type: none"> ■ Minimal or no chronic symptoms day or night ■ Minimal or no exacerbations ■ No limitations on activities; no school/work missed ■ Maintain (near) normal pulmonary function ■ Minimal use of short-acting inhaled beta₂-agonist ■ Minimal or no adverse effects from medications
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Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV₁ is % predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta₂-agonists. Overreliance on short-acting inhaled beta₂-agonists (e.g., use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

Figure 1-2. Stepwise approach for managing asthma in adults and children older than 5 years of age: treatment.

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. NIH Publication 02-5074. Bethesda, MD: United States Department of Health and Human Services, 2003.

glucocorticoid receptors and synergistically prevent the release of inflammatory mediators.

Studies have also looked at adding leukotriene receptor antagonists or theophylline to inhaled corticosteroids. Although these combinations also improve asthma control, the evidence is not as substantial as the evidence supporting the addition of long-acting inhaled β_2 -agonists. A recent Cochrane review looked at randomized, placebo-controlled trials in patients older than age 2 with asthma and found that the addition of leukotriene modifiers to inhaled corticosteroids had a modest effect on improving lung function compared with monotherapy with inhaled corticosteroids. As a result of these findings, the expert panel modified the preferred therapy for the treatment for patients with moderate persistent asthma from previous guidelines. For adults and children older than age 5, it is now recommended that a combination of low- to medium-dose inhaled corticosteroids in conjunction with a long-acting inhaled β_2 -agonist be used for treatment. Studies of the combination therapy of inhaled corticosteroids and a long-acting inhaled β_2 -agonist in children younger than age 5 have not been conducted. Nevertheless, the expert panel's opinion supported using this combination therapy in this age group, which resulted in preferred therapy guidelines for this age group. The new preferred therapy is low-dose inhaled corticosteroids plus a long-acting inhaled β_2 -agonist or monotherapy with medium-dose inhaled corticosteroids. This recommendation is one of the differences that exist between the NAEPP and the GINA guidelines. Due to the lack of literature supporting combination therapy in children younger than age 5, the recommended therapy in the GINA guidelines for this age group is medium-dose inhaled corticosteroids, and combination therapy is listed under "other treatment options."

Acute Therapy NAEPP Guidelines

Management of asthma exacerbations includes inhaled short-acting β_2 -agonists, systemic corticosteroids, inhaled ipratropium, and supplemental oxygen. For emergency department or hospital-based care, the NAEPP Expert Panel recommends albuterol nebulizer solution 2.5–5 mg every 20 minutes for three doses, then 2.5–10 mg every 1–4 hours as needed. The Update on Selected Topics 2002 did not make any changes from the previous guidelines on treating asthma exacerbations at home (Figure 1-3) or in the emergency department or hospital (Figure 1-4).

Delivery of albuterol by a metered-dose inhaler is also an option if the patient is able to coordinate inhalation of drug from a metered-dose inhaler. The recommended dose of albuterol in a metered-dose inhaler is 4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed. Traditionally, patients who present to an emergency department with an asthma exacerbation are treated with a nebulized β_2 -agonist. A recent Cochrane review evaluated 22 trials comparing the use of holding chambers and nebulizers for β_2 -agonists delivery in the management of acute asthma in adults and children. Reviewers concluded that the method of β_2 -agonist delivery did not affect the rate

of hospital admission. Of interest, the length of stay in the emergency department was significantly shorter in children using a holding chamber than in those using nebulizers.

Antibiotic Drug Use

The Drug Update on Selected Topics 2002 reviewed clinical trials to assess the possible benefit of antibiotic drug therapy in treating exacerbations of asthma. The recommendation does not change from the previous guidelines. Antibiotic drugs are not recommended for treating acute asthma exacerbations unless the patient presents with a fever, evidence of pneumonia, purulent sputum, or suspected bacterial sinusitis.

Special Populations

Pregnancy

The NAEPP has also updated the guidelines for treating asthma during pregnancy, *Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004*. The treatment goal for managing pregnant women with asthma is to continue optimal therapy to maintain control. The goals of asthma therapy in pregnant women are defined the same as in patients who are not pregnant. Also, it is safer for pregnant women and the fetus to be treated with drugs than to experience asthma symptoms and exacerbations.

The NAEPP report on managing asthma during pregnancy includes a stepwise approach, similar to that for the general treatment of asthma, for choosing the best pharmacological treatment (Figure 1-5). Preferred therapy includes using inhaled corticosteroids for patients with mild, moderate, or severe persistent asthma, and all patients should receive a short-acting inhaled β_2 -agonist. Albuterol is the preferred short-acting inhaled β_2 -agonist because it has the most data available on use during pregnancy and an excellent safety profile.

Among inhaled corticosteroids, budesonide is the steroid of choice because it has the most data on its use during pregnancy. In addition, budesonide has a pregnancy category B rating. However, the guidelines point out that data do not exist to indicate that any of the inhaled corticosteroids are unsafe for use during pregnancy. As a result, the guidelines recommend that if a woman is well controlled on an inhaled corticosteroid other than budesonide before pregnancy, she may continue that inhaled corticosteroid during pregnancy.

The NAEPP guidelines for treating asthma during pregnancy also include management strategies for asthma exacerbations for home treatment, emergency department, and hospital care (Figures 1-6 and 1-7). Due to the potential for asthma exacerbations to lead to serious consequences for the fetus, the guidelines recommend aggressive management with a short-acting inhaled β_2 -agonist and oral corticosteroids.

Devices

Metered-dose Inhalers

In 2005, the Food and Drug Administration announced that the production and sale of single-ingredient albuterol metered-dose inhalers that contain chlorofluorocarbons will stop December 31, 2008. The Food and Drug

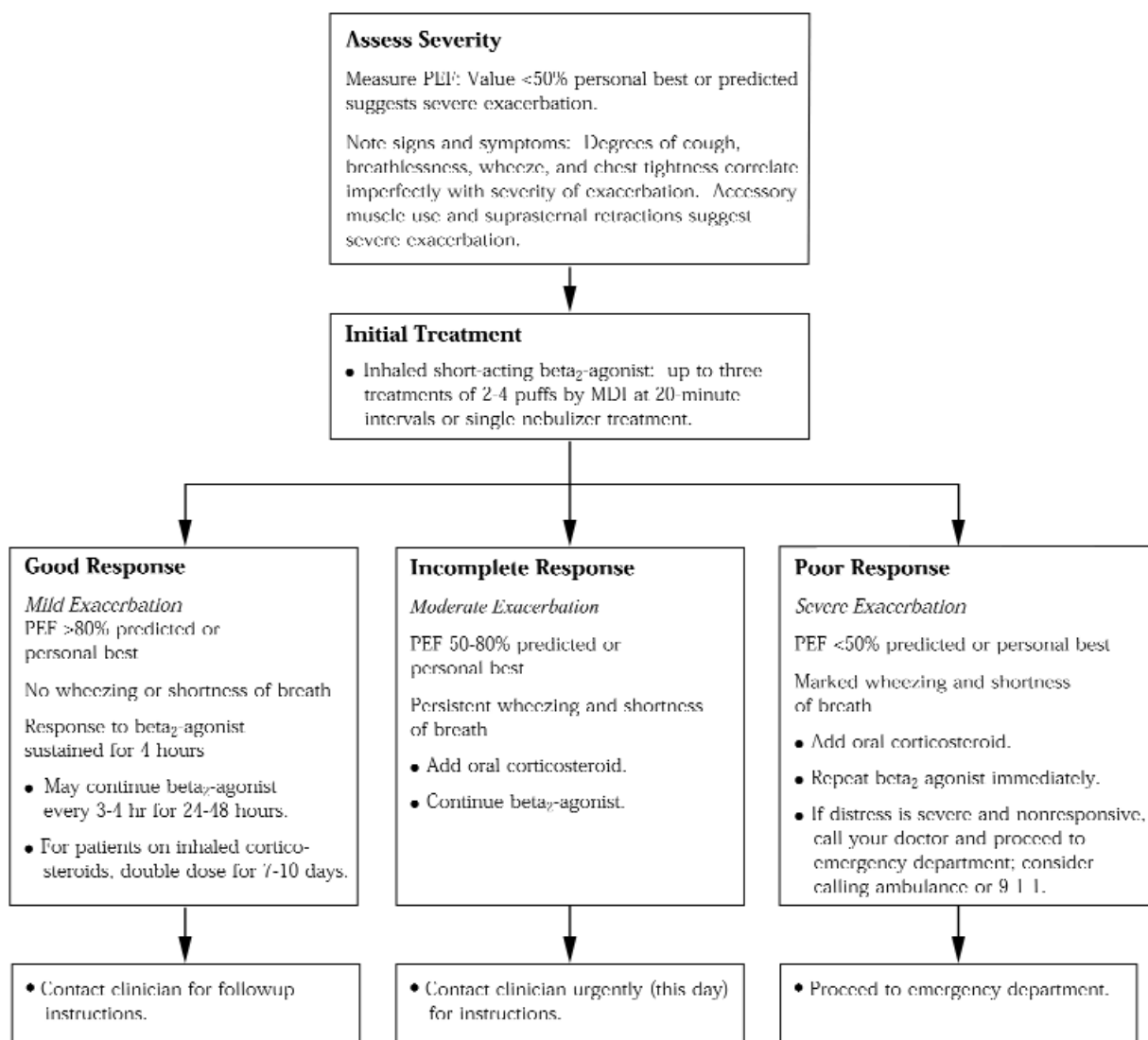


Figure 1-3. Management of asthma exacerbations: home treatment.

MDI = metered-dose inhaler; PEF = peak expiratory flow.

National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report (EPR-2). Guidelines for the Diagnosis and Management of Asthma. NIH Publication 97-4051. Bethesda, MD: United States Department of Health and Human Services, 1997.

Administration Advisory Committee considers the Ventolin HFA and Proventil HFA sufficient alternatives to albuterol metered-dose inhalers containing chlorofluorocarbons. However, the cost of the HFA-containing products is significantly higher than the cost of the albuterol metered-dose inhaler. To ease this transition, manufacturers of the HFA-containing products are implementing programs to ensure that cost will not be a barrier to patients. The suggested programs include giving inhalers away and offering cost-saving coupons and assistance based on the patient's financial need.

Dry Powder Inhalers

The Aerolizer is one of the newest dry powder inhaler devices to become available in the United States. The only drug available for use with this device is formoterol fumarate. This plastic device is used to inhale formoterol

fumarate contained in a capsule. The capsule is placed in the device and is pierced by pressing and releasing the buttons located on the side of the device. Similar to other dry powder inhalers, the drug is inhaled with a rapid and deep inhalation. The amount of drug delivered to the lungs depends on the inspiratory rate and inspiratory duration. Studies have demonstrated that about 90% of patients older than age 5 can generate the minimum inspiratory flow required for this device.

Monitoring

Patients with asthma should be monitored to ensure that they are achieving their therapy goals. Pharmacists can monitor patients in a variety of ways, including assessing symptom history, monitoring adherence to and adverse effects of drugs, and assessing patients' ability to use devices (Figure 1-8). Because pharmacists are often the

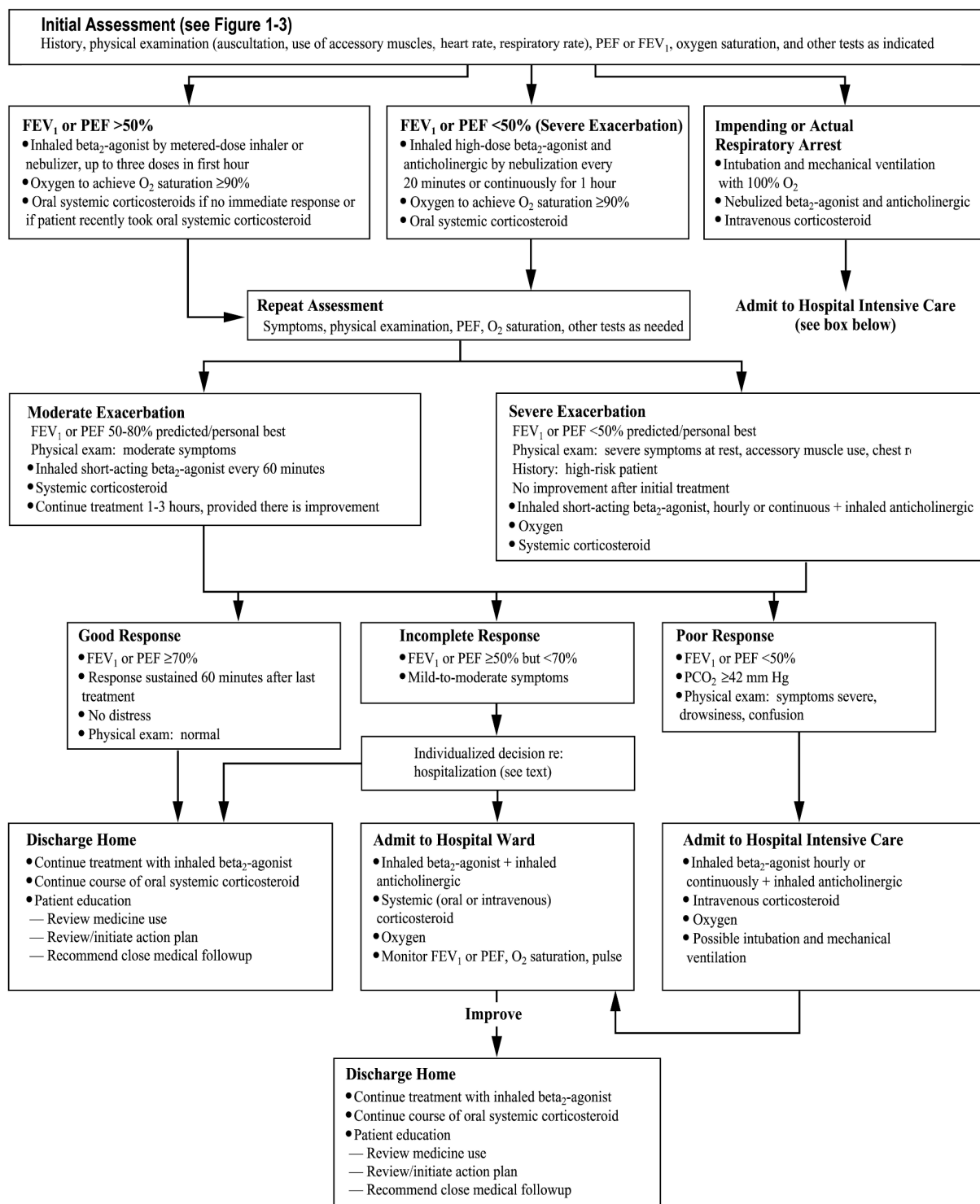




Figure 1-4. Management of asthma exacerbations: emergency department and hospital-based care.

FEV₁ = forced expiratory volume in 1 second; O₂ = oxygen; PEF = peak expiratory flow.

National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report (EPR-2). Guidelines for the Diagnosis and Management of Asthma. NIH Publication 97-4051. Bethesda, MD: United States Department of Health and Human Services, 1997.

Classify Severity: Clinical Features Before Treatment or Adequate Control			Medications Required To Maintain Long-Term Control
	Symptoms/ Day	PEF or FEV ₁	Daily Medications
	Symptoms/ Night	PEF Variability	
Step 4 Severe Persistent	Continual	≤60%	<ul style="list-style-type: none">Preferred treatment:<ul style="list-style-type: none">High-dose inhaled corticosteroid ANDLong-acting inhaled beta₂-agonist AND, if needed,Corticosteroid tablets or syrup long term (2 mg/kg per day, generally not to exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroid and maintain control with high-dose inhaled corticosteroid.*)Alternative treatment:<ul style="list-style-type: none">High-dose inhaled corticosteroid* ANDSustained release theophylline to serum concentration of 5–12 mcg/mL.
	Frequent	>30%	
Step 3 Moderate Persistent	Daily	>60%–<80%	<ul style="list-style-type: none">Preferred treatment: EITHER<ul style="list-style-type: none">Low-dose inhaled corticosteroid* and long-acting inhaled beta₂-agonist ORMedium-dose inhaled corticosteroid.*If needed (particularly in patients with recurring severe exacerbations):<ul style="list-style-type: none">Medium-dose inhaled corticosteroid* and long-acting inhaled beta₂-agonist.Alternative treatment:<ul style="list-style-type: none">Low-dose inhaled corticosteroid* and either theophylline or leukotriene receptor antagonist.†If needed:<ul style="list-style-type: none">Medium-dose inhaled corticosteroid* and either theophylline or leukotriene receptor antagonist.†
	>1 night/week	>30%	
Step 2 Mild Persistent	>2 days/week but <daily	≥80%	<ul style="list-style-type: none">Preferred treatment:<ul style="list-style-type: none">Low-dose inhaled corticosteroid.*Alternative treatment (listed alphabetically): cromolyn, leukotriene receptor antagonist† OR sustained-release theophylline to serum concentration of 5–12 mcg/mL.
	>2 nights/month	20%–30%	
Step 1 Mild Intermittent	≤2 days/week	≥80%	<ul style="list-style-type: none">No daily medication needed.Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroid is recommended.
	≤2 nights/month	<20%	
Quick Relief All Patients	<ul style="list-style-type: none">Short-acting bronchodilator: 2–4 puffs short-acting inhaled beta₂-agonist‡ as needed for symptoms.Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroid may be needed.Use of short-acting inhaled beta₂-agonist‡ >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.		

	Step down Review treatment every 1–6 months; a gradual stepwise reduction in treatment may be possible.
	Step up If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.
Goals of Therapy: Asthma Control	
<ul style="list-style-type: none"> Minimal or no chronic symptoms day or night Minimal or no exacerbations No limitations on activities; no school/work missed 	<ul style="list-style-type: none"> Maintain (near) normal pulmonary function Minimal use of short-acting inhaled beta₂-agonist‡ Minimal or no adverse effects from medications

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is percent of personal best; FEV₁ is percent predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroid), then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta₂-agonist‡ (e.g., use of approximately one canister a month even if not using it every day indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy).
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens, irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if Step 4 care is required. Referral may be considered if Step 3 care is required.

* There are more data on using budesonide during pregnancy than on using other inhaled corticosteroids.

† There are minimal data on using leukotriene receptor antagonists in humans during pregnancy, although there are reassuring animal data submitted to FDA.

‡ There are more data on using albuterol during pregnancy than on using other short-acting inhaled beta₂-agonists.

Figure 1-5. Stepwise approach for managing asthma during pregnancy and lactation: treatment.

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—2004 Update. NIH Publication No. 05-3279. Bethesda, MD: United States Department of Health and Human Services, 2005.

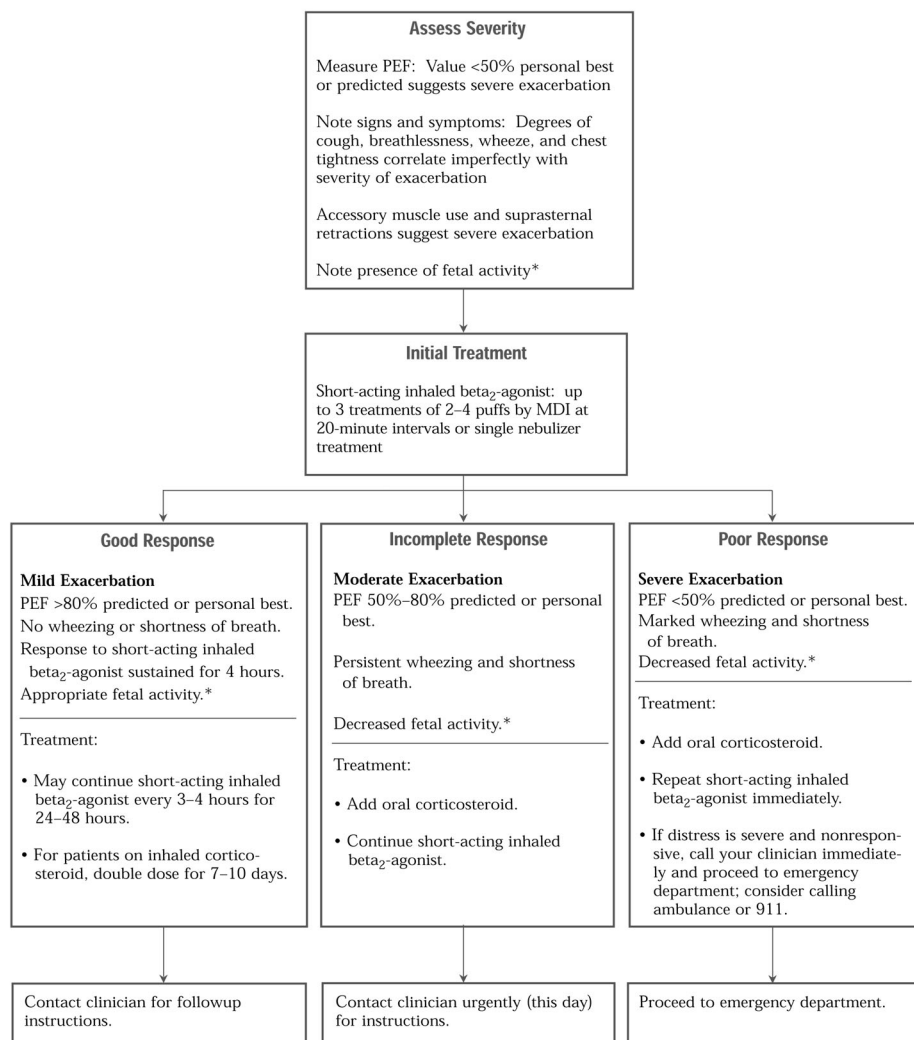


Figure 1-6. Management of asthma exacerbations during pregnancy and lactation: home treatment.

*Fetal activity is monitored by observing whether fetal kick counts decrease over time.

MDI = metered dose inhaler; PEF = peak expiratory flow.

National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Managing Asthma during Pregnancy: Recommendations for Pharmacologic Treatment—2004 Update. NIH Publication No. 05-3279. Bethesda, MD: United States Department of Health and Human Services, 2005.

health care providers who interact most frequently with patients, they are frequently able to assess a patient's ability to use different devices. Assessment of patients' symptoms should include questions about daytime and nocturnal symptoms. Information regarding exacerbations, oral steroid use, and emergency department visits or hospitalizations for asthma should also be ascertained. Many pharmacists have immediate access to a patient's drug refill history, which allows them to quickly assess adherence to long-term control therapies and overuse of a short-acting inhaled β_2 -agonist.

Indicators that a patient's asthma is not under control include awakening at night with asthma symptoms, having an urgent care visit for asthma, having an increased need for a short-acting inhaled β_2 -agonist, or using more than one canister per month of a short-acting inhaled β_2 -agonist. For a patient with uncontrolled asthma, several things

should be checked before increasing the dose or adding more therapies, including inhaler technique, adherence to drugs, and environmental changes.

Health care providers should review a patient's treatment every 1–6 months. When control has been achieved and maintained, a gradual decrease in therapy should be considered. If control is not achieved or maintained, an increase in therapy is necessary. These changes should be based on the stepwise approach for managing asthma (see Figures 1-1, 1-2, and 1-5).

The most effective way for patients to monitor their asthma symptoms has long been an area for discussion. The validity of peak flow monitoring and action plans based on peak flow readings or symptoms in both children and adults have all been questioned. Thorough literature evaluations by the NAEPP expert panel and several Cochrane reviews have been completed to help answer these questions.

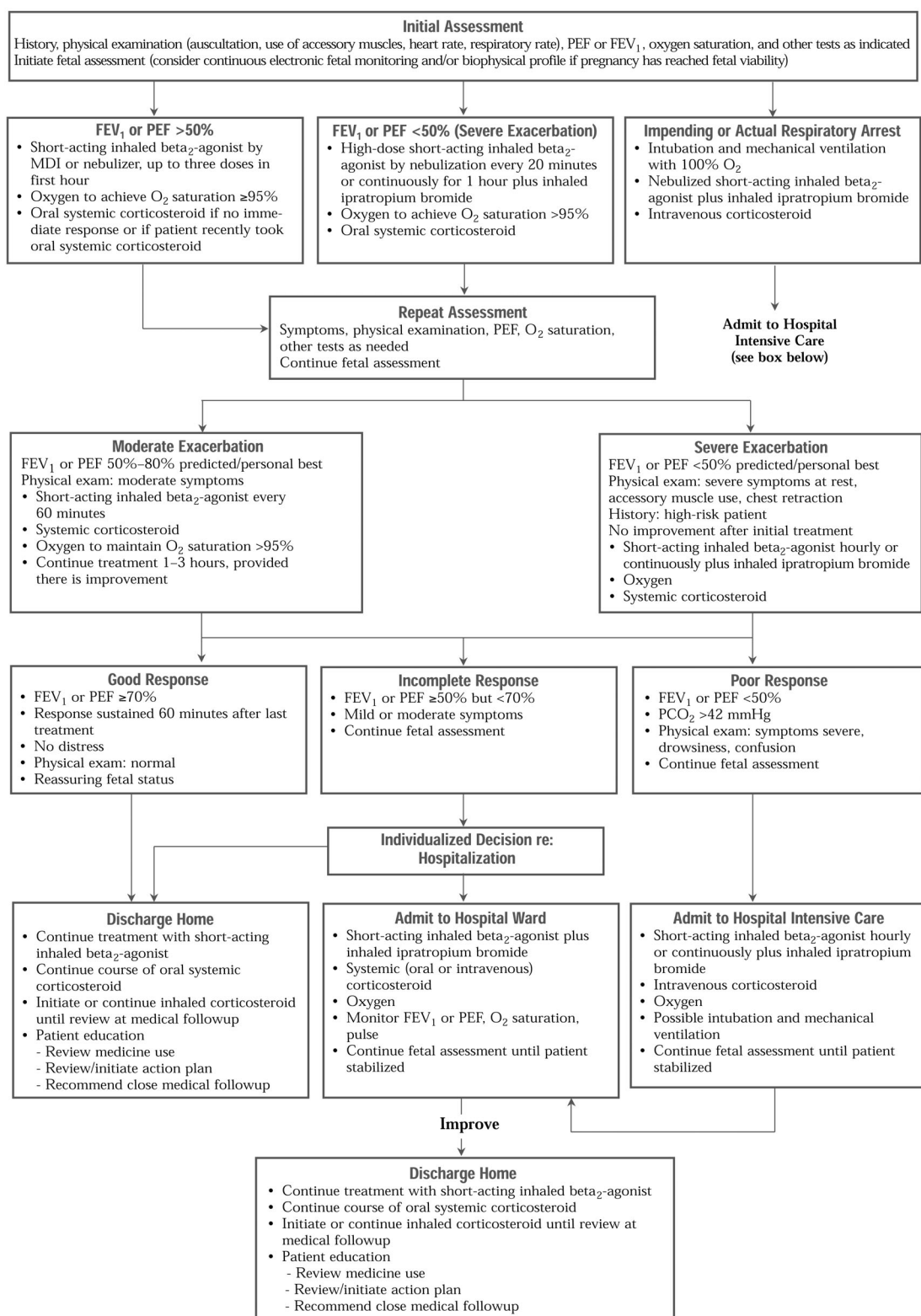


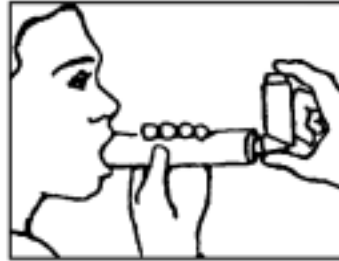
Figure 1-7. Management of asthma exacerbations during pregnancy and lactation: emergency department and hospital-based care. FEV₁ = forced expiratory volume in 1 second; MDI = metered-dose inhaler; O₂ = oxygen; PCO₂ = carbon dioxide partial pressure; PEF = peak expiratory flow.

National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—2004 Update. NIH Publication No. 05-3279. Bethesda, MD: United States Department of Health and Human Services, 2005.

1. Remove the cap and hold inhaler upright.
2. Shake the inhaler.
3. Tilt your head back slightly and breathe out slowly.
4. Position the inhaler in one of the following ways (A or B is optimal, but C is acceptable for those who have difficulty with A or B. C is required for breath-activated inhalers):



A. Open mouth with inhaler 1 to 2 inches away.



B. Use spacer/holding chamber (that is recommended especially for young children and for people using corticosteroids).



C. In the mouth.
Do not use for corticosteroids.



D. NOTE: Inhaled dry powder capsules require a different inhalation technique. To use a dry power inhaler, it is important to close the mouth tightly around the mouthpiece of the inhaler and to inhale rapidly.

5. Press down on the inhaler to release medication as you start to breathe in slowly.
6. Breathe in slowly (3 to 5 seconds).
7. Hold your breath for 10 seconds to allow the medicine to reach deeply into your lungs.
8. Repeat puff as directed. Waiting 1 minute between puffs may permit second puff to penetrate your lungs better.
9. Spacers/holding chambers are useful for all patients. They are particularly recommended for young children and older adults and for use with inhaled corticosteroids.

Avoid common inhaler mistakes. Follow these inhaler tips:

- Breathe out before pressing your inhaler.
- Inhale slowly.
- Breathe in through your mouth, not your nose.
- Press down on your inhaler at the start of inhalation (or within the first second of inhalation).
- Keep inhaling as you press down on inhaler.
- Press your inhaler only once while you are inhaling (one breath for each puff).
- Make sure you breathe in evenly and deeply.

Figure 1-8. Steps for using your inhaler.

National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report (EPR-2). Guidelines for the Diagnosis and Management of Asthma. NIH Publication 97-4051. Bethesda, MD: United States Department of Health and Human Services, 1997.

Written Action Plans

One of the questions reviewed by the Update on Selected Topics 2002 regarding monitoring was whether written asthma action plans improved outcomes compared with medical management alone. The expert panel concluded that the available data are insufficient to adequately answer this question. They also stated that a significant number of studies looking at this question were poorly designed. However, the expert panel continues to support using written action plans to educate patients in the self-management of asthma. A recent Cochrane review also tried to answer this question. This review looked only at

randomized, controlled trials in which the patient was assigned to receive a written action plan (either peak flow-based or symptom-based) or no written management plan. The review found seven studies meeting the inclusion criteria and concluded that the trials conducted were too small and results too inconsistent to reach a firm conclusion.

Peak Flow and Symptom-based Action Plans

A second question the Update on Selected Topics 2002 addressed regarding patient monitoring was whether symptom-based or peak flow-based written action plans result in greater improvement in asthma outcomes. Once

again, few studies were available for evaluation, and those that were had study design flaws making it impossible to come to any valid conclusions. As a result, the NAEPP expert panel did not change its recommendation from the previous guidelines and continues to support the consideration of using peak flow monitoring for patients with moderate and severe persistent asthma.

Exhaled Nitric Oxide

A continuing area of study has been the significance of exhaled nitric oxide and its association with asthma severity and symptoms. The fractional concentration of exhaled nitric oxide is increased in patients with asthma compared with patients who do not have asthma. In addition, nitric oxide concentrations are decreased with corticosteroid use. Exhaled nitric oxide is a marker of airway inflammation caused by asthma. It has also been found to correlate with histamine and methacholine airway reactivity, and responsiveness to bronchodilators. Consistent correlations between exhaled nitric oxide, lung function, and asthma severity have not been found. The NIOX Nitric Oxide Test System (Aerocrine AB, Sweden) is an exhaled nitric oxide monitoring system for clinical use. This device received a label indication by the Food and Drug Administration in 2003 for monitoring response to anti-inflammatory drugs as an adjunct to established clinical and laboratory assessments. Ongoing studies are attempting to determine if adjunctive monitoring of exhaled nitric oxide improves outcomes in asthma. Handheld devices for home monitoring of exhaled nitric oxide are being developed.

An area of research that has been receiving greater emphasis is measuring markers of inflammation in exhaled breath condensate. Several markers are being studied, including interleukins 1β , 8, 10 and 6, tumor necrosis factor- α , leukotrienes, and pH. Although investigations are showing promise that this may be a noninvasive way to monitor anti-inflammatory therapy as well as airway inflammation, not enough data exist to make any conclusions.

Pharmacoeconomic and Quality of Life Assessments

Few pharmacoeconomic studies have compared the cost-effectiveness of asthma drugs. Although randomized, controlled, double-blinded, clinical trials are necessary for determining the efficacy and safety of a drug, extracting data from these trials for pharmacoeconomic modeling would result in inaccurate results due to their strict criteria and monitoring. Studies using clinical and administrative databases have yielded useful results. However, these studies have potential for investigator bias (e.g., selection of inclusion and exclusion criteria and statistical methods) and the potential for misinterpretation of the retrospective data. Retrospective database studies comparing inhaled corticosteroids to leukotriene modifiers universally confirm the results observed in randomized, clinical trials that inhaled corticosteroids are more cost-effective. The addition

of a long-acting inhaled β_2 -agonist to inhaled corticosteroid is more cost-effective than the addition of a leukotriene receptor antagonist.

Two areas that have received attention regarding costs in the treatment of acute severe asthma are the use of levalbuterol and the use of a metered-dose inhaler compared with a nebulizer for the delivery of short-acting inhaled β_2 -agonists. Studies examining the cost-effectiveness of levalbuterol have been poorly done and difficult to interpret. Investigators have used the cost of levalbuterol specific for their institutions, which are contract-dependent, making it difficult to apply the results to a broad setting. Studies comparing the use of metered-dose inhalers to nebulized treatments have also been difficult to interpret because the issue of labor costs was not adequately addressed.

Quality of life assessments are frequently included in clinical research; however, these assessments are not made in the majority of clinical practices, possibly because clinicians are not aware of the instruments and possibly due to time constraints.

Patient Education

Patient education has long been a cornerstone to optimize patient outcomes. The NAEPP has defined several areas that should be addressed to ensure that patients adequately understand their disease and are empowered to take control of their disease. The educational message should include discussion of disease pathophysiology, roles of the different drugs, skills necessary to optimize drug delivery, effectiveness of specific environmental control measures, and when and how to take rescue drugs.

Incorporating environmental control measures into an asthma management plan is recommended by NAEPP and should be emphasized during the education process. In a questionnaire-based study of parents with children with asthma, the most common triggers for asthma were plants (34%), animals (31%), dust (29%), weather/change of season (27%), and smoke (24%). The majority of parents (81%) had incorporated at least one environmental control action. Researchers determined that of parents who pursued an environmental control action, about 51% of the actions taken were not likely to be useful for the intended trigger. Increased education and re-enforcement on environmental control are necessary for patients and their families. Pharmacists can help patients determine their specific triggers and educate them on the most effective measures to minimize their effect.

The World Health Organization has estimated that patient adherence to long-term therapy for chronic illnesses is about 50%. Nonadherence rates for asthma range from 30% to 70%. Patient nonadherence is responsible for increased morbidity and mortality in patients with asthma. Patients may decide to be nonadherent with their drug regimen for a variety of reasons, including forgetfulness, failure to understand the specifics of the regimen, or

Cabana MD, Slish KK, Lewis TC, et al. Parental management of asthma triggers within a child's environment. *J Allergy Clin Immunol* 2004;114:352-7.

World Health Organization. Adherence to Long-term Therapies: Evidence for Action. Geneva, Switzerland: WHO, 2003. Available at http://www.who.int/chronic_conditions/adherencereport/en/. Accessed December 14, 2005.

purposely not taking the drug. Pharmacists can improve patient adherence by developing a partnership with their patients and educating their patients on the roles and actions of their drugs. Pharmacists improve patient adherence by working with patients to develop reminders on when to take their drugs and by coordinating dosing regimens that accommodate schedules for work, school or other activities. Pharmacists can also recommend less costly drugs and periodically review drugs to prevent therapeutic duplication.

After reviewing 36 studies, the Cochrane group concluded that education that includes asthma self-management based on peak flow or symptom monitoring, plus regular medical evaluation and written action plans, will improve health outcomes. The outcomes that improved were reductions in hospitalizations, emergency department visits, unscheduled doctor visits, days missed from work or school, and nocturnal asthma symptoms. A patient's quality of life also improved.

Pharmacists are in a position to improve patient outcomes by addressing this aspect of patient care. Pharmacists can assess their patients' knowledge of asthma, educate them on the role and appropriate use of drugs, advise on environmental control measures, and educate them on the appropriate use of rescue drugs.

Quality Improvements

The care of patients with asthma is undergoing continuous quality improvement from a variety of perspectives. The NAEPP is convening an expert panel to perform another critical review of the literature to update the guidelines for the management of asthma, which should be available in 2006.

The extent to which asthma and other respiratory diseases have become a public health issue has attracted the attention of several federal agencies in the United States. Healthy People 2010 has included respiratory diseases as one of its new focus areas with several objectives related to the well-being of patients with asthma. Specific objectives addressed by Healthy People 2010 include reducing the number of deaths attributed to asthma, reducing hospitalization due to asthma, reducing emergency department visits, reducing limitations of activities, and reducing the number of days missed at school or work. Other objectives include increasing the number of patients who receive formal asthma education, increasing the number of patients who are receiving appropriate care based on the NAEPP guidelines, and establishing surveillance systems for tracking asthma deaths, illness, disability, impact of occupational and environmental factors on asthma, access to medical care, and asthma management.

In addition to the activities associated with asthma on the national level, several organizations are allowing practitioners to become specialized in the care of asthma. The National Asthma Educator Certification Board has developed an asthma educator certification examination to promote optimal asthma management and quality of life for

patients with asthma. Completion of this process certifies that the health care provider has achieved certain levels of experience and education. This examination is open to a variety of disciplines, including pharmacists.

Conclusion

Asthma is a complicated disease in which patients can present in a variety of ways. The exact cause of the disease has not been identified although inflammation is thought to play a central role. Treatment with drugs is the primary way for patients to achieve the goals of leading a normal lifestyle. Pharmacists can contribute to the well-being of patients with asthma in a variety of ways. This includes assessing the appropriate choice of drugs and potential adverse effects. Pharmacists can also provide education to patients regarding their disease, including pathophysiology of asthma, the roles of the different drugs, skills necessary to optimize drug delivery, effectiveness of specific environmental control measures, and when and how to take rescue drugs.

Annotated Bibliography

1. National Asthma Education and Prevention Program. NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. *J Allergy Clin Immunol* 2002;110:s141–219.

This document is an update of the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program (NAEPP) Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma, which was published in 1997. Similar to previous updates, the NAEPP convened an expert panel and used an evidence-based review of the literature to arrive at its conclusions. The Update on Selected Topics 2002, however, is written in a format different from the previous guidelines and is used in conjunction with the 1997 guidelines as opposed to completely replacing them. Rather than being a complete revision of previous guidelines, it addresses seven specific questions that the NAEPP expert panel believed deserved an extensive review based on the amount of research activity and concerns that had arisen from clinical practice. These questions concern the drugs, management, and prevention of asthma. The full text document thoroughly explains the specific strategies used for the literature evaluation and nicely documents the evaluated studies in a table format. In addition to the full document, the NAEPP has also developed a six-page Quick Reference document that summarizes the questions and answers from the complete text and gives the stepwise approach to treating asthma in useful figures. Both documents are available on the National Heart, Lung, and Blood Institute Web site at www.nhlbi.nih.gov/guidelines/asthma/index.htm.

2. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report—Update on Selected Topics 2 (EPR-2). Guidelines for the Diagnosis and Management of Asthma. NIH Publication

97-4051. Bethesda, MD: United States Department of Health and Human Services, 1997.

This document is used in conjunction with the National Asthma Education and Prevention Program's Expert panel report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002 to diagnose and treat patients with asthma. Similar to other NAEPP guidelines, an evidenced-based literature review was performed to arrive at the conclusions presented in this document. The guidelines are divided into four components: 1) measures of assessment and monitoring, 2) control of factors contributing to asthma severity, 3) pharmacological therapy, and 4) education for a partnership in asthma care. All of the components are extensively discussed and presented in a user-friendly manner. The document is available on the National Heart, Lung and Blood Institutes Web site at www.nhlbi.nih.gov/guidelines/asthma/index.htm.

3. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—2004 Update. NIH Publication No. 05-3279. Bethesda, MD: United States Department of Health and Human Services, 2005.

This document updates the 1993 Report of the Working Group on Asthma and Pregnancy. These guidelines were developed by a working group of experts on asthma and pregnancy who were given the charge by the NAEPP. As with other NAEPP guidelines, an evidence-based review was conducted, and recommendations were based on these findings. The literature search included both human and animal studies. Although the guidelines focus on the pharmacological treatment of asthma during pregnancy and lactation, they also include portions of the Expert Panel Report 2: Guidelines for the Diagnosis and Treatment of Asthma and the Update on Selected Topics 2002, which the working group deemed necessary to ensure the safety and successful management of asthma during pregnancy. Similar to the general guidelines, treating asthma during pregnancy involves determining the severity of asthma and choosing treatment in a stepwise fashion. The guidelines also thoroughly review the literature available for each of the drug classes. This document is also available in an easy-to-read format. In addition to the full report document, the NAEPP has developed a shorter Quick Reference report. The NAEPP has also supplied the tables that outline the studies evaluated for evidence. All three of these documents can be found on the NHLBI Web site at <http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm>.

4. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005;127:335–71.

This thorough review evaluates the available literature looking at inhalation device selection, and its effects on the efficacy and adverse effects of treatment. The aim of this guideline is 2-fold: to compare the efficacy and adverse effects of a variety of inhaled drugs given by different devices in specific populations and clinical settings, and to provide delivery device recommendations for specific populations. The authors evaluated randomized, controlled trials in humans, which were published in English. Based on the evaluated literature, the authors provide results and offer recommendations for device selection and use in a variety of settings and populations, including inpatient and outpatient settings and patients who are mechanically ventilated or have

asthma or chronic obstructive pulmonary disease. This well-written, evidenced-based document could benefit health care professionals taking care of patients requiring inhalation therapy.

5. Weinberger M, Murray MD, Marrero DG, et al. Effectiveness of pharmacist care for patients with reactive airways disease: a randomized controlled trial. *JAMA* 2002;288:1594–1602.

In this randomized, controlled trial conducted at 36 chain pharmacies, the authors' objective was to assess the effectiveness of a pharmaceutical care program for patients who had asthma or chronic obstructive pulmonary disease. Patients with active pulmonary disease were randomized to receive a pharmaceutical care intervention, a peak flow intervention, or usual care. For pharmaceutical care intervention, the pharmacists were trained in pharmaceutical care and its application to pulmonary disease; oriented to a study computer and access to patient-specific clinical data; trained in interpreting patient data and use of a peak flow meter; and provided with written education materials for patients as well as the resources to implement the program. The peak flow intervention consisted of the patient receiving a peak flow meter, instructions on its use, and monthly calls to obtain the peak flow information. The usual care group did not receive a peak flow meter or instructions on its use. The primary outcomes measured were peak expiratory flow rate, emergency department or hospital visits, health-related quality of life, drug compliance, and patient satisfaction. More than 1000 patients were enrolled with about 900 still participating 12 months into the study. At 12 months, patients who had received the pharmaceutical care intervention had increased peak expiratory flow rates compared with the usual care group but not the peak flow intervention group. The pharmaceutical care group also had increased patient satisfaction but increased expenditures for pulmonary-related medical care. The mixed results of this study have generated discussion about the implementation of a pharmaceutical care program in a community pharmacy. A variety of problems with the study design have been identified, such as the inclusion of both patients with asthma and chronic obstructive pulmonary disease, diseases that require different management strategies. A second issue of implementing a pharmaceutical care intervention without addressing the current structure of workload and work flow in a community pharmacy has also made the application of the results questionable. The lack of documentation performed by the pharmacist on interventions is also a reason for questioning the final results. The numerous issues regarding the design and results of this study have generated discussion on more appropriate study design to test the implementation of a pharmaceutical care intervention.

6. McFadden ER. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168:740–59.

This complete review on acute severe asthma begins by discussing the epidemiology and natural history of severe asthma. It progresses into a discussion on the clinical aspects, including pathology, clinical features, differential diagnosis and evaluation. The author thoroughly addresses the management of acute asthma in terms of genetic concerns and reviews specific therapies. It also reviews using more controversial therapies, including heliox and magnesium sulfate. The primary benefits of this review are the thoroughness and the author's expertise in treating severe acute asthma.

7. GlaxoSmithKline. The Salmeterol Multicenter Asthma Research Trial (SMART). GlaxoSmithKline (SLGA5011). Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4148B1_03_02-FDA-SMART-Study.pdf. Accessed November 18, 2005.

This was a 28-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of salmeterol plus usual asthma care and placebo plus usual asthma care. Patients were included if they were at least 12 years old and using a prescription asthma drug. Patients were excluded if they had ever used salmeterol or formoterol. The primary end point of this study was the combined number of respiratory deaths or life-threatening experiences. Secondary end points included combined asthma-related deaths and life-threatening experiences. The study consisted of a single clinic visit and follow-up phone calls every 4 weeks. During the clinic visit, eligibility status was determined, baseline data was collected, and patients were randomized to treatment. About 60,000 patients were to participate, and a planned interim analysis was to be conducted when about 50% of patients were enrolled. At the interim analysis, 26,355 had enrolled in the study with 13,176 in the salmeterol group. Demographic and baseline characteristics were similar in both groups. A statistically significant difference was not found between the two treatment groups in the primary end point (relative risk = 1.3952 and 95% confidence interval = 0.9097–2.1398). When looking at the combined number of respiratory deaths or life-threatening events by ethnicity, African-American patients in the salmeterol group experienced a statistically significantly higher frequency than in the placebo group (relative risk = 4.0997; 95% confidence interval = 1.5414–10.9042). A difference was not found between the two treatments in Caucasian subjects. When looking at the secondary outcomes, there was a statistically significant greater risk of the combined asthma-related deaths or life-threatening experiences in the salmeterol group compared with placebo. The salmeterol group had 37 events while the placebo group had 22 events (relative risk = 1.7068; 95% confidence interval = 1.0075–2.8912). A statistically significant difference in the incidence of asthma-related death between the groups was also found. Thirteen events occurred in the salmeterol group and three events in the placebo group (relative risk = 4.3715; 95% confidence interval = 1.2460–15.3367). Although analysis by ethnic origin did not show statistically significant differences between treatment with salmeterol and treatment with placebo for asthma-related deaths, African Americans being treated with salmeterol had more events (7 in 2366 patients) than those treated with placebo, 1 event in 2319 patients (relative risk = 7.2580; 95% confidence interval = 0.8937–58.9439). Caucasians treated with salmeterol also had a higher number of asthma-related deaths when compared with placebo (6 events in 9281 vs. 1 event in 9361, relative risk = 5.8247; 95% confidence interval = 0.7014–48.3707). Overall inhaled corticosteroid use was reported to be 47% (49% of Caucasian population and 38% of African American population). Asthma-related deaths were lower in subjects receiving inhaled corticosteroids (seven events) compared with subjects not receiving inhaled corticosteroids (nine events). Asthma-related deaths occurred more frequently in subjects who did not use inhaled corticosteroids but did receive salmeterol. This finding was seen in both Caucasian and African-American patients. Adherence to the drug was not monitored during this study. Although not reaching the predetermined criteria for stopping the study, the company terminated the study due to difficulties with recruitment of, and the findings in, African-American patients. The results of this study led to the inclusion of a box warning in the labeling

of products containing salmeterol stating that a placebo-controlled United States trial showed a small but significant increase in asthma deaths.

8. Blue Cross and Blue Shield Association Technology Evaluation Center. Management of chronic asthma. Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality, 2001.

The National Heart, Lung, and Blood Institute in conjunction with the Agency for Healthcare Research and Quality, contracted the Blue Cross Blue Shield Association Technology Evaluation Center to conduct a systematic review of the evidence used by the NAEPP expert panel to make recommendations in the Update on Selected Topics 2002. This document reviews the search methodology and results. The report succinctly summarizes all of the studies reviewed and provides evidence tables with study design, research variables and outcomes while also providing a narrative on the results. This report can be downloaded from the following Web site at <http://www.ahrq.gov/clinic/evrptfiles.htm>.