ASTHMA: An Update on Management
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Needs Statement:
Asthma is one of the most common chronic diseases in the United States and it is associated with significant morbidity, mortality and expense. The disease can substantially interfere with an individual’s daily activities and is responsible for missed school and work, clinic and emergency department visits, and almost a half-million hospitalizations each year. Associated costs approach $20 billion annually. Currently therapies directed at the disease’s primary components, inflammation and hyperresponsiveness, are available and able to improve disease control and improve patients’ quality of life when appropriately utilized. Additionally, the morbidity and mortality of asthma can be positively impacted through patient education on the factors related to asthma and appropriate medical management. These outcomes are dependent upon health professionals maintaining current knowledge of evidence-based guidelines that can be subsequently translated into the care and education of their patients.

Intended Audience:
This course is designed for physicians, pharmacists, nurse practitioners, nurses and other health professionals who treat or interact with patients with asthma.

Course Goal:
This educational monograph presents current information for health care professionals on the pathophysiology, diagnosis, treatment, and patient self-management of asthma. By learning and subsequently incorporating this information into practice, health professionals may provide better care and improve outcomes in asthma patients.

Objectives:
At the completion of this course the participant will be able to:

1. State the current definition of asthma and the role of inflammation in this disease process.
2. List patient factors that support the diagnosis of asthma.
3. Describe the classification of asthma and the pharmacologic management for each category.
4. Identify patient characteristics that warrant consultation with an asthma specialist.
5. List the goals of asthma therapy as identified by the Expert Panel on the Management of Asthma.
6. Recall the Expert Panel recommendations for management and monitoring of asthma during pregnancy.
7. Describe how periodic assessment and monitoring can determine if the goals of therapy are being met.
8. List six classes of pharmacologic agents used in asthma treatment, the mechanism of action and common side effects of each.
9. Justify the stepwise approach in the long-term management of asthma.
10. Name the important elements for successful early treatment of asthma exacerbations.
11. Describe the role of patient education in asthma self-management.

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INTRODUCTION

Asthma is one of the most common chronic diseases in the United States and it is associated with significant morbidity, mortality and expense. Information derived from the 1982-2006 National Health Interview Survey indicated nearly 34.1 million U.S. persons had reported a physician diagnosis of asthma during their lifetime. Of these, approximately 22.9 million Americans currently have asthma; 12.4 millions had an asthma attack in 2006. In the years between 1982 and 1996 asthma prevalence rates increased 59 per cent; rates declined from 2001-2004 before again increasing each year since 2004.1

Asthma is the leading chronic illness of children in the United States. In 2006 more than 6.8 million children under the age of 18 had asthma; 4.1 million had an asthma attack in 2006. Children 5-17 years of age (106.3 per 1000 population) had the highest prevalence rate. The rate in those less than 18 years of age is 92.8 per 1,000; in those 18-44 the rate is 72.4 per 1000. The prevalence rate is 46 per cent higher for boys ages 0-17 compared to girls in the same age range. Interestingly, beyond childhood, women are more likely to develop asthma than men. In 2006, nearly 10.2 million adult women aged 18 or older had asthma compared to 5.9 million adult men. The prevalence rate among adult women is 60 percent greater than the rate among adult men.1

Approximately 4,000 will die from asthma each year. Women die more frequently than men due to asthma and people over the age of 65 are much more likely to die from asthma compared to all other age groups, including young children. In 2005, health resource utilization information attributable to asthma included 12.8 million outpatient visits, 1.8 million emergency department visits, and 484,000 hospitalizations.1 Asthma can substantially interfere with an individual’s daily activities. In 2003, 12.8 million school days for children 5-17 years of age and 10.1 million work days for adults 18 and older were missed due to asthma. Associated annual asthma costs are estimated to be a staggering $19.7 billion. Direct health care costs total more than $14.7 billion and include over $6.2 billion for prescription drugs. Indirect costs (lost productivity) are approximately $5 billion. Associated morbidity and mortality can be positively impacted through patient education on the factors related to asthma and appropriate medical management.6 Despite a better understanding of the condition’s pathogenesis and availability of improved treatments, these asthma related problems persist.6

In 1991 the National Asthma Education and Prevention Program (NAEPP), established by the National Heart, Lung and Blood Institute (NHLBI), sponsored the first Expert Panel on the Management of Asthma. Their publication, Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma, redefined commonly held beliefs about asthma care. It set the stage for a national effort to improve the clinical management of asthma and stimulated related novel research.

In August 2007 NAEPP issued a comprehensive update of the clinical guidelines for the diagnosis and management of asthma. This follows the 1997 release of the Expert Panel Report 2 (EPR-2) that furthered the understanding of the pathogenesis of asthma and increased knowledge of effective approaches to its diagnosis, monitoring, pharmacologic and environmental management, and patient education. The Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma is the most contemporary, comprehensive, accurate source of information for clinicians on asthma diagnosis and management.4 The guidelines focus on four key areas of asthma care: 1) measures to assess and monitor asthma, 2) patient education, 3) control of environmental factors and other conditions that can worsen asthma, and 4) medications. It is the goal of the NAEPP to broadly disseminate and encourage implementation of these recommendations. It is hoped that statistics on asthma associated morbidity and mortality, which have yet to reflect positively on the acquisition of improved knowledge and treatments, may begin to do so. In accordance with the ambition to bridge the gap between current knowledge and practice in the management of asthma, this course will be based on the recommendations of EPR-3 emphasizing patient education at every step of clinical asthma care and by all members of the health care team.

ASTHMA: AN INFLAMMATORY DISEASE

DEFINITION

Asthma is defined as: a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.5 Subbasement membrane fibrosis may occur in some patients with asthma, which contributes to persistent abnormalities in lung function.6
PATHOGENESIS

Airflow restriction in asthma is recurrent and caused by a variety of changes in the airway that include: bronchoconstriction, airway edema, airway hyperresponsiveness and airway remodeling. Airway inflammation, whether acute or chronic, is a constant feature in the various types of asthma.

The first evidence characterizing asthma as a chronic inflammatory disease was obtained from post-mortem examinations on patients with asthma. Generally, these airways contained plugs of mucus, serum proteins, inflammatory cells and cellular debris. Microscopically, smooth muscle hypertrophy, thickening of the basement membrane and an inflammatory infiltrate composed primarily of eosinophils but also neutrophils, lymphocytes, and mononuclear cells were observed. Inflammatory changes have been noted in bronchial biopsy specimens from patients with mild or asymptomatic asthma. These include denuded epithelial membrane, increased collagen deposition below the basement membrane, as well as increased inflammatory cell infiltrates. Eosinophils, mast cells, and epithelial cells are more prevalent in the bronchoalveolar lavage of asthmatics than in those without the disease.

The definition of asthma notes that airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in characteristic pathophysiologic features of the disease. These are: bronchial inflammation and airflow limitation that cause recurrent episodes of cough, wheeze and shortness of breath.

Inflammatory mediators that injure airway tissues. Subpopulations of T lymphocytes (TH2) regulate allergic inflammation in the airway through the release of chemokines and cytokines (including interleukin-4 and interleukin-5) which play a role in also establishing disease chronicity. Fibroblasts, endothelial, and epithelial cells of the airway also contribute to this process through cytokine and chemokine release.

Inflammatory mediators include chemokines, TH2-derived cytokines, cysteiny1 leukotrienes, and nitric oxide. The mediators affect smooth muscle tone, modulate vascular permeability, activate neurons, stimulate mucus secretions, and cause structural changes in the airway. They can injure ciliated airway epithelium and cause epithelial cells and myofibroblasts to proliferate and start deposition of interstitial collagens in the lamina reticularis of the basement membrane. This may explain apparent basement membrane thickening and the irreversible airflow changes that occur in some asthma patients.

Airway inflammation is present in all asthma regardless of severity. It is thought to be acute, subacute or chronic. Early recruitment of cells to the airway represents the acute response. Recruited and resident cell activation causing a more persistent pattern of inflammation is characteristic of the subacute type. A persistent level of cell damage and ongoing repair are traits of chronic inflammation.

The relationship between airway inflammation and airway responsiveness is complex. Airway hyperresponsiveness correlates with the presence of inflammatory markers. Marker reduction through asthma treatment has been shown to reduce symptoms but affect airway responsiveness variably. Factors other than inflammation may contribute to airway hyperresponsiveness.

Airflow obstruction in asthma is recurrent and has various causes. Acute bronchoconstriction can result from airway smooth muscle contraction from histamine, tryptase, leukotrienes, and prostaglandins after an IgE-dependent release from the mast cells. Nonsteroidal anti-inflammatory drugs can also cause acute airflow obstruction through a non-IgE-dependent release of mediators from airway cells. Other less understood mechanisms of acute airflow obstruction can result from exercise, cold air, irritants, and other stimuli. The intensity, however, appears to be related to underlying airway inflammation. Swollen airway walls and mucosal thickening, resulting from increases in mediator influenced microvascular permeability, interfere with airflow whether smooth muscle contraction is present or not. Mucus plug formation, associated with severe asthma, can cause persistent airflow restrictions. Finally, airway remodeling, which occurs in some asthmatic patients, contributes to airflow limitations. This process, involves an alteration in the amount and composition of the extracellular matrix in the airway wall. This change appears to be only partially...
reversible and may explain the persistent nature of obstruction and unresponsiveness to treatment seen in some patients. Remodeling may be associated with longstanding and severe airway inflammation, mucus hypersecretion, subepithelial fibrosis and smooth muscle hypertrophy. Consequently, some feel this justifies early intervention with anti-inflammatory therapy in asthma.

Asthma begins most frequently in childhood and adolescence. In children, it is often associated with atopy, a genetic tendency to produce IgE to common environmental allergens such as house-dust mites, animal proteins, and fungi. Allergens may also be associated with adult-onset asthma. In non-allergic individuals, sinusitis, nasal polyps, and sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs may be observed. Workplace materials, including animal products, biological enzymes, plastic resin, wood dusts (particularly cedar), and metals, have also been shown to cause airway inflammation, bronchial hyperresponsiveness, and clinical signs of asthma.19-20

Table 1. DIFFERENTIAL DIAGNOSTIC POSSIBILITIES FOR ASTHMA

<table>
<thead>
<tr>
<th>Infants and Children</th>
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<tbody>
<tr>
<td>Upper airway disease</td>
</tr>
<tr>
<td>• Allergic rhinitis and sinusitis</td>
</tr>
<tr>
<td>Obstructions involving large airways</td>
</tr>
<tr>
<td>• Foreign body in trachea or bronchus</td>
</tr>
<tr>
<td>• Vocal cord dysfunction</td>
</tr>
<tr>
<td>• Vascular rings or laryngeal webs</td>
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<tr>
<td>• Laryngotracheomalacia, tracheal stenosis, or bronchostenosis</td>
</tr>
<tr>
<td>• Enlarged lymph nodes or tumor</td>
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<tr>
<td>Obstructions involving small airways</td>
</tr>
<tr>
<td>• Viral bronchiolitis or obliterative bronchiolitis</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td>• Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>• Heart disease</td>
</tr>
<tr>
<td>Other causes</td>
</tr>
<tr>
<td>• Recurrent cough not due to asthma</td>
</tr>
<tr>
<td>• Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease (chronic bronchitis or emphysema)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Laryngeal dysfunction</td>
</tr>
<tr>
<td>Mechanical obstruction of the airways (benign and malignant tumors)</td>
</tr>
<tr>
<td>Pulmonary infiltration with eosinophilia</td>
</tr>
<tr>
<td>Cough secondary to drugs (e.g., angiotensin-converting enzyme [ACE] inhibitors)</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
</tr>
</tbody>
</table>

ASSESSMENT AND MONITORING

INITIAL ASSESSMENT AND DIAGNOSIS OF ASTHMA

The Expert Panel has offered guidelines to assist in diagnosing asthma. Clinicians should 1) determine the presence of episodic symptoms of airflow obstruction, 2) show that the obstruction is at least partially reversible, and 3) eliminate alternative diagnoses (Table 1). Because signs and symptoms may vary widely, even within a given patient, clinical judgment must be applied to the medical history, physical examination, and pulmonary function tests for a correct diagnosis. Additional studies may be necessary to eliminate other diagnoses, identify precipitating factors, assess severity, or determine complications. Symptoms that are considered primary indicators of asthma include:

- wheeze on exhalation
- cough that worsens at night
- recurrent chest tightness or difficult breathing
- reversible airflow limitation and diurnal variation indicated by peak expiratory flow (PEF), such as a PEF that is significantly better after an inhaled short-acting beta2-agonist (SABA) or markedly different in the AM compared to the PM reading

In asthma, symptoms tend to occur or worsen at night and when exposed to airborne particles of mold, pollen, house-dust mites, animal dander, smoke and various chemicals. Menses, highly emotional states, exercise and viral infections may precipitate or worsen existing symptoms. Table 2 lists sample questions that can be used in the initial assessment of patients presenting with asthma symptoms. Eczema, hay fever, or a family history of asthma or atopic diseases are

Table 2. SAMPLE QUESTIONS* FOR THE DIAGNOSIS AND INITIAL ASSESSMENT OF ASTHMA

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

In the past 12 months:

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

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

- at night that has awakened you?
- in the early morning?
- after running, moderate exercise, or other physical activity?

*Example questions; validity and reliability have not been assessed.
frequently associated with asthma, but are not considered primary indicators. The probability of asthma increases in individuals with multiple symptoms.

The medical history for a patient known or thought to have asthma should address the items listed in Table 3. Symptoms attributed to asthma, associations that strengthen the likelihood of asthma (e.g., patterns, family history), symptom severity and precipitating factors may be revealed by the medical history.

**Table 3. SUGGESTED ITEMS FOR MEDICAL HISTORY**

<table>
<thead>
<tr>
<th>A detailed medical history of the new patient who is known or thought to have asthma should address the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Symptoms</strong></td>
</tr>
<tr>
<td>a. Cough</td>
</tr>
<tr>
<td>b. Wheezing</td>
</tr>
<tr>
<td>c. Shortness of breath</td>
</tr>
<tr>
<td>d. Chest tightness</td>
</tr>
<tr>
<td>e. Sputum production</td>
</tr>
<tr>
<td><strong>2. Pattern of Symptoms</strong></td>
</tr>
<tr>
<td>a. Perennial, seasonal, or both</td>
</tr>
<tr>
<td>b. Continual, episodic, or both</td>
</tr>
<tr>
<td>c. Onset, duration, frequency (number of days or nights, per week or month)</td>
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<tr>
<td>d. Diurnal variations, especially nocturnal and on awakening in early morning</td>
</tr>
<tr>
<td><strong>3. Precipitating and/or aggravating factors</strong></td>
</tr>
<tr>
<td>a. Viral respiratory infections</td>
</tr>
<tr>
<td>b. Environmental allergens, indoor (e.g., mold, house-dust mite, cockroach, animal dander or secretory products) and outdoor (e.g., pollen)</td>
</tr>
<tr>
<td>c. Exercise</td>
</tr>
<tr>
<td>d. Occupational chemicals or allergens</td>
</tr>
<tr>
<td>e. Environmental change (e.g., moving to new home; going on vacation; and/or alterations in workplace, work processes, or materials used)</td>
</tr>
<tr>
<td>f. Irritants (e.g., tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases, and aerosols)</td>
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<tr>
<td>g. Emotional expressions (e.g., fear, anger, frustration, hard crying or laughing)</td>
</tr>
<tr>
<td>h. Drugs (e.g., aspirin; beta-blockers, including eye drops; non-steroidal anti-inflammatory drugs; other)</td>
</tr>
<tr>
<td>i. Food, food additives, and preservatives (e.g., sulfites)</td>
</tr>
<tr>
<td>j. Changes in weather, exposure to cold air</td>
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<tr>
<td>k. Endocrine factors (e.g., menses, pregnancy, thyroid disease)</td>
</tr>
<tr>
<td>l. Comorbid conditions (e.g., sinusitis, rhinitis, GERD)</td>
</tr>
<tr>
<td><strong>4. Development of disease and treatment</strong></td>
</tr>
<tr>
<td>a. Age of onset and diagnosis</td>
</tr>
<tr>
<td>b. History of early-life injury to airways (e.g., bronchopulmonary dysplasia, pneumonia, parental smoking)</td>
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<tr>
<td>c. Progression of disease (better or worse)</td>
</tr>
<tr>
<td>d. Present management and response, including plans for managing exacerbations</td>
</tr>
<tr>
<td>e. Need for oral corticosteroids and frequency of use</td>
</tr>
<tr>
<td>f. Frequency of using SABA</td>
</tr>
<tr>
<td><strong>5. Family history</strong></td>
</tr>
<tr>
<td>a. History of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives</td>
</tr>
</tbody>
</table>

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6. **Social History**

- Characteristics of home including age, location, cooling and heating system, wood-burning stove, humidifier, carpeting over concrete, presence of molds or mildew
- Characteristics of rooms where patient spends time (e.g., bedroom and living room with attention to bedding, floor covering, stuffed furniture)
- Smoking (patient and other in home or day care)
- Day care, workplace, and school characteristics that may interfere with adherence
- Social factors that interfere with adherence, such as substance abuse
- Social support/social networks
- Level of education completed
- Employment (if employed, characteristics of work environment)

7. **Profile of typical exacerbation**

- Usual prodromal signs and symptoms, rapidity of onset, duration, frequency, severity
- Usual patterns and management (what works?)

8. **Impact of asthma on patient and family**

- Episodes of unscheduled care (emergency department, urgent care, hospitalization)
- Life-threatening exacerbations (e.g., intubation, intensive care unit admission)
- Number of days missed from school/work
- Limitation of activity, especially sports and strenuous work
- History of nocturnal awakening
- Effect on growth, development, behavior, school or work performance, and lifestyle
- Impact on family routines, activities, or dynamics
- Economic impact

9. **Assessment of patient’s and family’s perceptions of disease**

- Patient, parental, and spouse’s or partner’s knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment
- Patient perception and beliefs regarding use and long-term effects of medications
- Ability of patient and parents, spouse, or partner to cope with disease
- Level of family support, patient’s and parents’, spouse’s, or partner’s capacity to recognize severity of an exacerbation
- Economic resources
- Sociocultural beliefs

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*This is not a standardized assessment or diagnostic instrument; validity and reliability has not been assessed.*
Spirometry is used to determine if airflow obstruction exists and if it is reversible over a short period of time. It should be used in patients in whom the diagnosis of asthma is being considered.\textsuperscript{21,22} It has been useful in children as young as four but depends on their ability to conduct the maneuver adequately. Measurements (FEV\textsubscript{1}, FVC, FEV\textsubscript{1}/FVC) are made before and after the patient inhales a short-acting bronchodilator. FVC, or forced vital capacity, is the maximal volume of air forcibly exhaled from the point of maximal inhalation. FEV\textsubscript{1} represents the volume of air exhaled during the first second of the FVC.

FEV\textsubscript{1} and FEV\textsubscript{1}/FVC values less than reference or predicted values indicate airflow obstruction. Following an inhalation of a short-acting bronchodilator, an increase of greater than or equal to 12 percent in FEV\textsubscript{1} from baseline or an increase greater than or equal to the predicted FEV\textsubscript{1} indicates significant reversibility. Occasionally, a trial of oral corticosteroid therapy may be necessary to demonstrate reversibility.

The EPR-3 has added a new emphasis on using FEV\textsubscript{1}/FVC to classify severity in children because it may be a more sensitive measure than FEV\textsubscript{1}. The Expert Panel recommends that office based physicians caring for asthma patients have access to spirometry for use in diagnosis and periodic monitoring. Technique as well as equipment calibration and maintenance are important to quality results. Adherence to standards developed by the American Thoracic Society (1995) is advocated.

Training courses in the performance of spirometry that are approved by the National Institute for Occupational Safety and Health (www.cdc.gov/niosh/topics/spirometry) are available. Severe abnormalities in office spirometry warrant further assessment in a specialized pulmonary function laboratory.

Other pulmonary function tests may be necessary, particularly in patients with coexisting chronic obstructive pulmonary disease (COPD), a restrictive defect, or possible central airway obstruction. Diffusing capacity tests are useful in smokers and elderly patients and those at risk for both emphysema and asthma. Peak flow monitoring can establish peak flow variability and define severity in symptomatic patients with normal spirometry. Assessment of diurnal variation or bronchoprovocation with methacholine, histamine or exercise may also be required.

Chest radiography, allergy testing, examination of the nose for nasal polyps and sinuses for disease, or evaluation for gastroesophageal reflux may be useful in some patients with asthma symptoms. Bronchoprovocation may be useful when spirometry results are unclear and should only be done by specially trained persons in appropriately equipped facilities.

Recurrent episodes of cough and wheezing are almost always due to asthma in children and adults. Other causes of airway obstruction manifested by wheezing must be considered. Infants frequently wheeze with acute upper respiratory viral infection because of small airways. Vocal cord dysfunction can mimic asthma and should be suspected when physical examination reveals a monophonic wheeze heard loudest over the glottis.

Once diagnosed, the severity of asthma is classified according to clinical manifestations (Table 4). Asthma severity is the intrinsic intensity of the disease. Specific measures for classifying severity include: symptoms, use of SABA for quick relief, exacerbations and lung function. Previous Expert Panel Reports included mild intermittent as the Step 1 category. The EPR-3 changed the category of mild intermittent to intermittent in order to emphasize that even patients who have intermittent asthma may have severe exacerbations.

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms**</th>
<th>Nighttime Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Persistent</td>
<td>• Daily symptoms</td>
<td>Daily</td>
<td>• FEV\textsubscript{1} or PEF &lt; 60% predicted</td>
</tr>
<tr>
<td></td>
<td>• Very limited physical activity</td>
<td></td>
<td>• PEF variability &gt; 30%</td>
</tr>
<tr>
<td></td>
<td>• Frequent exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Persistent</td>
<td>• Daily symptoms</td>
<td>&gt; 1 time a week but not nightly</td>
<td>• FEV\textsubscript{1} or PEF &gt; 60% - &lt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>• Daily use of inhaled short-acting (\beta_2)-agonist</td>
<td></td>
<td>• PEF variability &gt; 30%</td>
</tr>
<tr>
<td></td>
<td>• Some limitation with activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Persistent</td>
<td>• Symptoms &gt; 2 times a week but &lt; 1 time a day</td>
<td>3-4 times a month</td>
<td>• FEV\textsubscript{1} or PEF &gt; 80% predicted</td>
</tr>
<tr>
<td></td>
<td>• Minor limitation with activity</td>
<td></td>
<td>• PEF variability 20-30%</td>
</tr>
<tr>
<td>Intermittent</td>
<td>• Symptoms ≤ 2 times a week</td>
<td>≤ 2 times a month</td>
<td>• FEV\textsubscript{1} or PEF 80% predicted</td>
</tr>
<tr>
<td></td>
<td>• Asymptomatic and normal PEF between exacerbations</td>
<td></td>
<td>• PEF variability &lt; 20%</td>
</tr>
<tr>
<td></td>
<td>• Exacerbations brief (few hours to a few days); Intensity may vary</td>
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</tbody>
</table>

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

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

Table 4. CLASSIFICATION OF ASTHMA SEVERITY BEFORE TREATMENT: \(>12\) YEARS OF AGE AND ADULTS°
Asthma classifications are utilized to direct treatment and monitor disease progression/regression.

The severity classification, as evidenced in Table 4, is defined in terms of impairment and risk. These two terms are utilized to emphasize the need to consider asthma’s effects on quality of life (QOL) and functional capacity as well as the risks that asthma presents for future adverse events, such as exacerbations and progressive loss of lung function.

Although much of the care for patients with asthma is directed by their primary care providers, referral to a pulmonologist or other physician specializing in the care of asthma may be necessary. Reasons for patient referral identified by the Expert Panel are:

- occurrence of life-threatening asthma exacerbation
- goals of asthma therapy not met after 3 to 6 months of treatment; earlier if patient unresponsive to therapy
- atypical signs and symptoms or problems in differential diagnosis
- other complicating condition or its diagnosis (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis, vocal cord dysfunction, gastroesophageal reflux [GERD], COPD)
- patient requires additional education and guidance on therapy, adherence, or allergen avoidance
- patient considered for immunotherapy
- patient with severe persistent asthma, requiring step 4 care (considered for patients requiring step 3 care)
- patient requires continuous oral corticosteroid therapy or high-dose inhaled corticosteroids or has required more than two bursts of oral corticosteroids in 1 year
- patient is under age 3 and requires step 3 or 4 care; consider if under age 3 and requires step 2 care or initiation of daily long-term therapy
- confirmation of a history that suggests an occupational or environmental inhalant or ingested substance is provoking or contributing to asthma; considering complexities of diagnosis, treatment, or the intervention in the work environment, may need specialist to manage co-manage with the primary care provider.

Psychiatric, psychosocial, and family problems can interfere with asthma therapy. Referral to a mental health professional should be considered if these factors appear to affect disease management.

PERIODIC ASSESSMENT AND MONITORING

The goals of asthma therapy identified by the Expert Panel are:

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) “normal” pulmonary function (e.g., PEF < 10-20% variability or > 80% of personal best)
- Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
- Prevent recurrent exacerbations of asthma; minimize the need for emergency department visits or hospitalizations
- Require infrequent use (less than or equal to 2 days a week) of inhaled SABA for quick relief of symptoms
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patient’s and families’ expectations of and satisfaction with asthma care and quality of life
- Prevent asthma-related death

Periodic assessment at 1 to 6 month intervals and monitoring of symptoms, pulmonary function, patient activity, exacerbations, drug therapy, and patient health care provider communication is necessary to determine whether the goals are being met. The patient’s self-assessment of the above should be coupled with the clinician’s evaluation in considering management changes. Patients or their caregivers should be educated to know symptom patterns that indicate poor asthma control. This information, and particularly the occurrence of daytime symptoms, nocturnal awakening due to symptoms, and early morning symptoms unrelieved 15 minutes after inhaling a SABA, should be communicated at each health care visit. Patient diaries can facilitate accurate communication in instances where recall might be a problem.

Questions for assessing and monitoring asthma control include asking the patient:

- Does asthma awaken you at night or early morning?
- Is more SABA needed than usual?
- Was urgent medical care needed for you asthma?
- Are you able to participate in usual and desired activities?
- Is your peak flow reading less than your usual readings?

Pulmonary function is most frequently followed with peak flow monitoring and spirometry. Those who have experienced a near-fatal asthma exacerbation and elderly patients may benefit most since they appear less likely to perceive airflow obstruction.

Spirometry is preferred over peak flow monitoring for diagnosing because it has quality checks which insures more precise data. Additionally, wide variability exists in published peak expiratory flow (PEF) reference values. The Panel also recommends lung function assessment with spirometry after treatment has started, and symptoms and PEF have stabilized, during times of progressive or prolonged loss of asthma control, and then repeated at least every 1 to 2 years. Spirometry can be used to validate peak flow readings and measure airway responses to increases or decreases in drug therapy.

Peak flow monitoring measures the PEF using a portable, inexpensive peak flow meter. It is a simple, quantitative and reproducible test capable of demonstrating the presence and severity of airflow obstruction. Peak flow monitoring is useful in short-term monitoring, managing exacerbations, and in
daily long-term monitoring. Patients can use it to determine what aggravates their asthma, to evaluate the need for treatment changes and as a prompt to seek emergency care. It can be a valuable method of self-monitoring which is an important component in the self-management of asthma. Peak flow meters function best as tools for ongoing monitoring, not diagnosis. Measurement of PEF is dependent on the effort and technique of the patient. Therefore, patients need instruction, demonstration, and frequent review of their technique.

The personal best peak flow measurement is used as a specific patient’s reference value. It is the highest number achieved by a patient using their own peak flow meter with at least two measurements taken daily over a 2 to 3 week period of good symptom control. Percentages of one’s personal best peak flow can be arranged into traffic light like zones with specific actions to take as directed in a written treatment plan at predetermined cut points. The green zone (80% or greater of personal best) indicates good control with no need for altering treatment. The yellow zone (50-79% of personal best) signals caution and indicates the need for prompt treatment with a SABA. The red zone designates a more emergent situation. PEF values here require immediate treatment with a SABA. Depending on severity of symptoms, communication with one’s doctor or an emergency department for further action, or an emergency department visit is in order. Symptoms may be included in the written action plan to further describe the zones and appropriate action to take.

Increases in PEF of 20% or greater after taking a SABA compared to pretreatment values may indicate the need for an adjustment in drug therapy to better control asthma symptoms. This demonstrates a significant degree of airflow obstruction reversal.

The Expert Panel evaluated seven intervention studies on the use of daily peak flow monitoring for asthma management and offered recommendations for peak flow monitoring. Patients with moderate-to-severe persistent asthma (Step 3 - 6) should have a peak flow meter at home and be taught to monitor their PEF. In exacerbations it can determine severity and guide therapeutic decisions. Long-term daily monitoring can assist in detecting early changes requiring treatment, evaluate responses to therapeutic changes, indicate severity in patients unaware of airflow obstruction, and offer a quantitative measure of existing impairment. In the absence of long-term daily peak flow monitoring, short-term (2-3 weeks) monitoring is recommended to evaluate responses to therapy, link changes in PEF to asthma triggers, and to establish the individual patient’s personal best PEF. Additionally, any patient experiencing severe exacerbations may benefit from peak flow monitoring.

Long-term peak flow monitoring is generally not recommended for patients with intermittent or mild persistent asthma (Step 1 & 2). Disadvantages of this method of monitoring include problems with compliance due to inconvenience and lack of motivation. If no action plan based on measurements exists, the patient may find the maneuver meaningless. Erroneous readings because of poor technique, misinterpretation, or device failure are also possible.

The effect asthma has on a patient’s normal activities influences their quality of life and should be evaluated periodically. Attention should be drawn to absences from work or school, reduced usual activities for patients, changed care giver activities (due to child’s asthma), and sleep disturbances attributable to asthma.

The Expert Panel recommends that clinicians instruct patients and their families to use a daily diary and/or periodic self-assessment forms to determine whether their asthma is well controlled. This information should be shared with their health provider at follow-up visits.

**CONTROL OF FACTORS CONTRIBUTING TO ASTHMA SEVERITY**

An important component in the long-term management of asthma is to avoid or minimize exposure to substances or factors, which cause or worsen symptoms. Possible offenders include inhaled allergens, animals, occupational and environmental irritants, and aggravating conditions or drug reactions.

Household allergens, which can be inhaled, are numerous. House-dust mites, cockroaches, fungi (mold), and substances from all warm-blooded animals, such as dander, urine, feces, and saliva can cause allergic reactions. In susceptible individuals increased airway inflammation and hyperresponsiveness has been demonstrated.26 Children with sensitivity to inhalant allergens are at risk for developing asthma.27 The role of inhalant sensitivity as a cause of asthma is less important in adults.28

Effective management requires identification of the responsible allergen(s). An organized inquiry is a good method to initiate the process of determining what an individual might be exposed to. Their medical history may be useful in revealing seasonal allergy problems. Skin testing or in vitro testing for the presence of IgE antibodies to seasonal or perennial allergens can narrow the investigation by demonstrating specific sensitivities. Finally, identified sensitivities to allergens must be linked to clinical symptoms. At this point, productive action may be taken to reduce relevant allergen exposure.

The Expert Panel recommends that all patients with asthma, regardless of severity, be questioned about exposure to inhalant allergens. Because sensitivity to allergens can worsen asthma symptoms and affect its management, they
recommend that all patients with persistent asthma who require daily therapy be evaluated to see if allergens contribute to their disease.

Occupational exposure to sensitizing chemicals or dusts can induce asthma. Suspicion is supported by the presence of symptoms at work and their absence while away. Patients may fail to recognize the inter-relationship with work because symptoms often begin several hours after exposure. Acute exposure to irritants can cause a reactive airway dysfunction syndrome that presents with symptoms similar to asthma.

Environmental irritants affect asthma morbidity and management. All asthma patients should avoid tobacco smoke. It is the most important environmental indoor irritant and is a major cause of asthma symptoms in children and adults. Likewise, asthma patients should limit their exposure to outdoor air pollutants and irritants. Respirable particulates, ozone, sulfur dioxide (SO₂), formaldehyde, volatile organic compounds (VOCs) and nitric oxide (NOₓ) may cause asthma symptoms. Fumes from un-vented gas, oil, or kerosene stoves, wood-burning appliances, sprays, and strong odors can irritate the lungs resulting in symptoms. The use of humidifiers is generally not recommended in homes of patients with asthma and who are sensitive to house-dust mites and mold. In susceptible individuals, outdoor activities may need to be avoided when levels of air pollution are increased.

Rhinitis, sinusitis, and viral respiratory infections are conditions that can aggravate asthma. Inflammation of the upper airway can lead to lower airway hyperresponsiveness and asthma symptoms. Treatment with intranasal corticosteroids reduces nasal inflammation, obstruction, and discharge resulting in reversal of lower airway symptoms. Antihistamines may relieve symptoms limited to the upper airways. Antibiotics can be used to treat complicating bacterial infections. Yearly influenza vaccinations are recommended for patients with persistent asthma because they may be at increased risk for complications should they contract the flu. Influenza vaccine does not appear to reduce either the frequency or severity of asthma exacerbations during the influenza season.

Asthma patients with recurrent heartburn, or sour/acidic spitting up, and those with frequent nocturnal asthma symptoms should be evaluated and, if necessary, treated for GERD. It is important that practitioners be mindful of the potential contribution of a related condition, laryngopharyngeal reflux (LPR), to asthma in that LPR may present with none of the symptoms typical of GERD. Reflux during sleep can contribute to nocturnal asthma.

Obesity has been associated with asthma in children and adults. Weight loss may contribute to improvement in pulmonary function and overall health. Patients who are concurrently overweight or obese and have unstable, not-well controlled asthma may have concurrent obstructive sleep apnea (OSA). Asthma and OSA may co-exist in large numbers of patients.

Adult patients with asthma, nasal polyps, and a history of bronchoconstriction after taking aspirin or other nonsteroidal anti-inflammatory drugs are at risk for severe or fatal reactions. Health care professionals should be alert to such patients. Affected patients should be informed of this possibility and advised to use aspirin alternatives such as acetaminophen or salazate.

Beta-blocker medications, including topical ophthalmic preparations can cause bronchial smooth muscle constriction. This is less likely to occur with cardio-selective beta-blockers, particularly if they are used in lower dosages. The selectivity is a relative characteristic that can be lost with higher dosages.

Patients with sensitivities to sulfite preservatives should avoid foods processed with them. This may include dried fruit, processed potatoes, beer or wine. Severe asthma exacerbations are possible in these individuals.

Observational studies have demonstrated an association between increased stress and psychological factors and an increase in the prevalence of asthma, occurrence of poorly controlled asthma, and as a factor precipitating asthma exacerbations. Controlled clinical trials are needed to verify these associations.

**PHARMACOLOGIC THERAPY:**

**THE MEDICATIONS**

Drugs are used in the management of asthma to control or prevent symptoms, improve quality of life, reduce the frequency and intensity of exacerbations, reverse airflow obstruction and decrease emergency care, hospitalizations and death. Therapeutic strategy is based upon the scientific evidence of associated pathology and involves two general categories of drugs, long-term-control and quick-relief medications. Long-term-control therapy, taken daily on a long-term basis to achieve and maintain control of persistent asthma, is directed toward the chronic inflammation of this airway disorder and the resulting symptoms of airflow limitation, mucus production, and cough. Corticosteroids (systemic and/or inhaled), cromolyn sodium and nedocromil, immunomodulators, long-acting-β₂-agonists (LABAs), methylxanthines, and leukotriene modifiers compose this group. Quick-relief medications provide rapid relief of bronchoconstriction, acute airflow obstruction and acute symptoms such as cough, chest tightness, and wheezing. These include SABAs, anticholinergics, and systemic corticosteroids. Patients with persistent asthma require both classes of medication.
Research for potential new treatments is focusing on the mechanisms of asthma pathophysiology. Because of the central role of cytokines derived from the TH2 lymphocyte in mediating many of the alterations observed in asthma, the potential to modify this through factors that control TH2 production, cytokine generation, and substances that attract TH2 cells into the airways are being explored. 

Current clinical trials are evaluating tacrolimus (inhibits T-lymphocyte activation), etanercept (blocks tumor necrosis factor), omalizumab (blocks IgE from binding to mast cells and basophils), and golimumab (antibody that blocks tumor necrosis factor alpha activity) in the treatment of asthma.

**Corticosteroids**

Corticosteroids are potent anti-inflammatory agents with application in quick-relief and long-term-control of asthma. In moderate-to-severe exacerbations, systemic corticosteroids hasten resolution of airflow obstruction and reduce the rate of relapse. Methylprednisolone, prednisolone, and prednisone are commonly used systemic corticosteroids.

In the long-term management of asthma inhaled forms are used to suppress a broad range of inflammatory processes which reduce symptoms, improve lung function (peak expiratory flow, spirometry), decrease airway hyperresponsiveness, prevent exacerbations and possibly affect airway wall remodeling. Inhaled corticosteroids (ICS) are the most effective, long-term therapy available for all forms of persistent asthma. Various oral inhalation preparations of beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, triamcinolone acetonide, and mometasone furoate are available. Ciclesonide is a new inhaled corticosteroid recently approved by the Food and Drug Administration (FDA) for the treatment of asthma. This drug is unique in that it is inactive until it reaches the lung where it is converted to its active form. Additionally, it has high protein binding, low oral bioavailability and rapid clearance. These factors might reduce its risk for local and systemic adverse events. Previously, it was available as a nasal spray and approved for allergic rhinitis.

These steroids are FDA approved for the maintenance and prophylactic treatment of chronic asthma. This includes use in patients who require systemic corticosteroids and may benefit from systemic dose reduction or elimination. Systemic corticosteroids can be used in short courses to gain prompt control of the disease when initiating long-term therapy or chronically in severe forms uncontrolled by inhaled high-dose steroids. Expert Panel-3 concludes that studies have demonstrated that inhaled corticosteroid therapy improves control more effectively in children and adults than any other long-term control medication.

The anti-inflammatory effects of corticosteroids are numerous, and complex. The airway epithelial cells appear to be important activity sites where steroids inhibit the expression of cytokines, granulocyte-macrophage colony-stimulating factor, lipid mediators, nitric oxide, adhesion molecules, and possibly inducible genes. Other inflammatory cell targets include macrophages, T lymphocytes, dendritic cells, and eosinophils. It is not known which of these actions is responsible for specific effects on asthma.

Systemic corticosteroids have widespread activity and many potential adverse effects. Prolonged use can cause adrenal axis suppression, bone growth retardation in children, osteoporosis, dermal thinning, hypertension, diabetes, Cushing’s syndrome, cataracts, muscle wasting and weakness, and immunosuppression. Disturbances in glucose metabolism, increased appetite, edema from sodium retention, mood alterations, and gastrointestinal disturbances, including peptic ulcer, may result from even short courses (3-10 days) of systemic steroids.

Systemic side effects from inhaled corticosteroids are much less likely, particularly with usual doses needed for asthma control. Swallowed drug and that absorbed from the lung are sources for systemic effects from inhaled steroids. This can be reduced by using spacer devices, rinsing and spitting after use, and selecting a steroid that undergoes extensive first-pass hepatic metabolism (budesonide, fluticasone propionate). Adverse effects associated with inhaled corticosteroids are generally limited to local effects. Oral candidiasis and dysphonia are common but may be minimized through spacers, mouth rinsing, and using at less frequent intervals (BID vs. QID). Reflex cough and bronchospasm can be reduced with slower rates of inspiration, spacer or holding chambers, or pretreatment with an inhaled beta2-agonist.

Treatment strategies minimizing systemic exposure and accompanying adverse effects should be observed with corticosteroids. This includes the chronic use of inhaled rather than systemic steroids and using the lowest effective dose possible. While most effects are dose dependent, it is important to know that inter-individual variation may cause effects in some at doses you generally wouldn’t expect. Addition of another drug class, such as a LABA, may accomplish asthma control without increasing the steroid dose. Although steroids may reduce linear growth in children, controversy is generated by factors such as variable growth patterns among children, short observation periods, the influence uncontrolled asthma has on growth, and data showing a delay rather than decreased growth. In late 1998 a joint panel of FDA advisers recommended stricter labeling regarding this side effect by manufacturers.

Chronic use of inhaled corticosteroids has been addressed in the 2002 EPR-Update and resulted in revision of recommendations for treating children with mild or moderate persistent asthma. Evidence demonstrates improved disease control in these children and that inhaled corticosteroids at
recommended doses do not significantly or irreversibly affect vertical growth, bone mineral density, ocular toxicity or suppress the hypothalamic-pituitary-adrenal (HPA) axis. Growth should continue to be monitored in children receiving corticosteroids by any route and the benefit vs. risk evaluated individually. Adults and particularly perimenopausal women may benefit from concurrent calcium and vitamin D to counter possible osteoporotic effects.

Cromones

The cromones, cromolyn sodium and nedocromil sodium are alternative, non-prescribed medications for the treatment of mild persistent asthma and as preventative treatment before exercise or exposure to precipitating allergens. Although the two compounds vary structurally, they have similar anti-inflammatory effects. The mechanism of action appears to involve blockade of swelling-dependent chloride channels to modulate mast cell mediator release and eosinophil recruitment.\(^{51}\) They inhibit the early and late response to allergen challenge and exercise-induced bronchospasm. Nedocromil is more potent on a weight basis than cromolyn and appears to affect a broader range of inflammatory cells. Additionally, it suppresses cough through inhibition of neuronal reflexes in airways; an activity not shared by cromolyn sodium.\(^{47}\) Both can reduce asthma symptoms, improve morning peak flow, and reduce quick-relief SABA use.\(^{52}\)

The cromone’s greatest advantage is the absence of significant adverse effects. Nedocromil causes an unpleasant taste in some and each is generally dosed four times daily which may be inconvenient. The cromones are less effective than inhaled corticosteroids. They appear most effective in mild persistent asthma, but in a variable, unpredictable manner. They also can be used as preventative treatment before exercise or unpreventable exposure to known precipitating allergens. Patients whose primary symptom is coughing may benefit most. Their effects are generally evident within two weeks, but may require four to six weeks for maximal benefit.

Immunomodulators

Omalizumab, a recombinant DNA-derived humanized monoclonal antibody, may be considered as adjunctive therapy for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of inhaled corticosteroids and a LABA.\(^{4}\) Omalizumab inhibits the binding of IgE to receptors on mast cells thereby leading to a decrease in the release of allergen-induced mediators.

Omalizumab has not been compared in clinical trials to other agents for moderate persistent asthma. Urticaria and anaphylaxis are complications of omalizumab administration.

The Expert Panel concludes that evidence does not support the use of methotrexate, cyclosporine, other monoclonal antibodies, IVIG or colchicine for asthma treatment.\(^{4}\)

Long-Acting Beta\(_2\)-Agonists

Long-acting beta\(_2\)-agonists (LABAs) promote bronchodilation and are used with anti-inflammatory drugs for long-term control of asthma symptoms. They are particularly useful with nocturnal symptoms and can be used in prophylaxis of exercise-induced bronchospasm. Salmeterol metered dose inhaler, formoterol fumarate dry powder inhalation (DPI) and solution for inhalation (solution not FDA approved for Asthma at publication date) and oral sustained release forms of albuterol are available sources of LABAs.

The primary action of beta\(_2\)-agonists is stimulation of the beta\(_2\)-receptors. In asthma, the target cells are the airway smooth muscle cells that express beta\(_2\)-receptors from the trachea to the terminal bronchioles.\(^{53}\) Receptor stimulation activates adenylate cyclase and increases cyclic adenosine monophosphate (cAMP), which is capable of reversing the effects of all bronchoconstrictor substances.\(^{54}\) Other airway cells may be affected by beta\(_2\)-agonists for a beneficial effect in asthma. Beta-adrenoreceptor stimulation may stabilize mast cells preventing the release of inflammatory mediators\(^{55}\) and inhibit cholinergic neuro-transmission reducing cholinergic-reflex broncho-constriction.\(^{56}\) The addition of LABAs to treatment regimens of patients whose asthma is not well controlled on low or medium dose ICS improves lung function, decreases symptoms, exacerbations and the need for use of SABAs for quick relief.

Beta\(_2\)-agonists are the most useful bronchodilators used to treat asthma. Their effect is greatest when inhaled with the drug reaching beneficial target cells more effectively.\(^{57}\) Side effects are common with systemic beta-adrenergic preparations because of stimulation of receptors in various tissues and organs throughout the body. They include muscle tremor, palpitations, tachycardia, and restlessness. These effects are minimized with inhalation preparations, but are dose related and increase with higher doses. Oral LABAs, which are short acting entities in a sustained release mechanism, share the side effect profile of the systemic preparations.

Inhaled LABAs are preferred over oral sustained-release preparations because they are longer acting, providing bronchodilation for up to 12 hours after a single dose; duration decreases with chronic use. The health professional must be aware of certain limitations and concerns regarding their use. Salmeterol is NOT to be used in treating acute symptoms or exacerbations because of its slow onset of action (15-30 minutes). Formoterol is also not intended for this use. In November of 2005 the FDA requested the manufacturers of the inhaled LABAs to add new warnings to their product information regarding their use in asthma (not applicable for exercise-induced wheezing or COPD) patients. Although the LABAs decrease the frequency of asthma episodes, it now appears they have the potential to make asthma episodes more severe when they do occur. In addition, asthma deaths occur more frequently during these
severe episodes when compared to patients who are treated with placebo. Consequently, users are to be informed not to use their LABAs to treat wheezing that is getting worse and to call their health care professional promptly if wheezing worsens while using a LABA. The mechanism by which LABAs produce asthma exacerbations has not been established. Also, these drugs should not replace anti-inflammatory therapy as they don’t possess this activity. The FDA requires a Black Box warning for all preparations containing a LABA.

As an add on therapy to inhaled corticosteroids, inhaled LABAs are superior to leukotriene antagonist in improving lung function and this combination is more effective than just increasing the ICS dose in improving asthma control. LABAs are the preferred treatment to combine with ICS in children over the age of 12 years and adults.

**Short-Acting Beta₂-Agonists**

Inhaled SABA is the therapy of choice for relief of acute symptoms of asthma. They prevent exercise induced bronchoconstriction but for a shorter time period compared to the LABAs.

LABAs have the same mechanism of action and potential side effects as LABAs previously described. The inhaled forms have a faster onset than oral preparations and fewer side effects. Solutions for nebulization or metered dose inhalers of albuterol, levalbuterol, pirbuterol, or terbutaline are preferred over preparations with less beta₂-agonist specificity, such as isoproterenol, metaproterenol, isoetharine, and epinephrine. Drugs in the later group are not recommended because of their likelihood of greater side effects associated with excessive cardiac stimulation (beta₁ agonist activity).

Therapeutic issues regarding beta₂-agonist safety and use, include tolerance and increased morbidity and mortality in asthmatics. Tolerance to the bronchoprotective effects of beta₂-agonists appears to develop with continual use. This phenomenon and its clinical relevance is not fully understood. Genetic differences in receptors, long-acting agonist vs. short, full-agonist vs. partial, possible steroid protection of receptor, and frequency of use are factors relating to tolerance that require further definition. All synthetic beta₂-agonists, except levalbuterol, exist as racemic mixtures with the R-enantiomer possessing the therapeutic activity. It has been suggested that the S-enantiomer may have negative effects on smooth muscle responsiveness. High doses and frequent use of short-acting beta₂-agonists have been associated with increased risks of death and morbidity from asthma. Controversy persists whether an inhaled beta₂-agonist has long-term adverse effects or if their high use indicates severe unstable asthma. Excessive use should serve as a marker of inadequate control and patients should be taught its significance since an increase in anti-inflammatory therapy will be needed.

**Methylxanthines**

Methylxanthines, theophylline being the most familiar in this class, have been used for over fifty years and once were the cornerstone of asthma therapy. Today, these mild-to-moderate bronchodilators are considered second or third line agents and are generally used in combination with inhaled corticosteroids for long-term control of symptoms associated with mild persistent asthma. They are especially useful for nocturnal symptoms. Drugs in this class may be an alternative in long-term preventative therapy to the preferred inhaled corticosteroids and LABAs when problems exist with their use.

Their action has not been fully defined but probably involves multiple mechanisms. Theophylline is a relatively weak smooth muscle relaxant which competitively inhibits phosphodiesterase, the enzyme that degrades cAMP. Increased intracellular levels of cAMP produce airway smooth muscle relaxation. However, usual levels of theophylline do not raise cAMP levels sufficiently to account for its activity. Inhibition of extracellular adenosine, which has bronchoconstrictive effects, may explain some of its activity. Theophylline appears to have mild immunomodulating or anti-inflammatory effects at doses lower then those required for bronchodilation. Lower doses of theophylline also block the late response to allergen and are associated with a decreased number of eosinophils in the airway. Control of activated lymphocyte movement in the airway contributes to the anti-inflammatory effect of theophylline. Theophylline has a potent effect on diaphragmatic contractility, through an unknown mechanism, which may affect fatigability.

Theophylline’s greatest advantage is that it can be conveniently taken orally and as infrequent as once or twice daily. Its convenience is somewhat diminished by the fact that serum concentrations must be periodically followed to prevent dose related toxicity. These effects are more likely as levels exceed 20 mcg/mL and include tachycardia, nausea, vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemeses, hyperglycemia, and hypokalemia. Adverse effects possible at usual therapeutic levels include insomnia, gastric upset, aggravation of ulcer or reflux, hyperactivity in some children, and difficult urination in elderly males with prostatism. Individual variation in metabolic clearance is significant and dietary and drug influences on absorption and metabolism are extensive. These factors make monitoring of levels necessary.

**Leukotriene Modifiers**

Leukotriene modifiers are considered as alternative options for prophylaxis and chronic treatment in patients with mild persistent asthma. These drugs are not used to treat acute asthma attacks. Further study is needed to define their complete role in asthma treatment. Drugs in this class reduce the effects of leukotrienes which participate in the pathophysiology of asthma. Leukotrienes are released from
mast cells, eosinophils, and basophils where they produce airway smooth muscle contraction, increase vascular permeability and mucus secretion, and attract and activate inflammatory cells in the airways. Leukotriene modifiers include leukotriene receptor antagonists (LTRA) and a 5-lipoxygenase pathway inhibitor.

Zafirlukast is an oral medication that is a leukotriene (LTD4 and LTE4) receptor antagonist and is approved for use in adults and children ≥ 5 years of age. It reduces the late response to inhaled allergen,68 and post-allergen induced bronchial responsiveness.69 Compared to placebo in mild-to-moderate asthma, zafirlukast improved FEV1 (mean 11%), improved symptom scores, and reduced albuterol (SABA) use (average 1 puff/day).70 It has no significant side effects. Zafirlukast influences hepatic CYP2C9 and CYP3A4 microsomal isoenzymes which makes certain drug interactions (e.g. increased warfarin levels, increased theophylline and decreased zafirlukast) possible and increases the need for monitoring. It should be taken on an empty stomach as its bioavailability is decreased with food. Clearance is decreased in the elderly and those with liver disease. Cases of hepatic dysfunction have occurred; most patients improve with discontinuation of zafirlukast. Some patients progress to fulminant hepatic failure resulting in transplant or death. Liver enzymes should be monitored.

Montelukast, a newer oral leukotriene receptor antagonist similar to zafirlukast, has the benefit of once daily dosing. Additionally, it can be given to children as young as 12 months old in the form of oral granules. It does not interact with theophylline or warfarin and has a side effect profile similar to placebo. Montelukast can be given without regard to meals as its bioavailability is not influenced by food.71,72

Zileuton is also an oral medication approved for use in adults and children ≥ 12 years of age but affects leukotrienes by a different mechanism. It suppresses their synthesis by inhibiting 5-lipoxygenase, an enzyme instrumental in the conversion of arachidonic acid to leukotriene. Immediate and sustained improvements in FEV1 (mean 15%) over placebo were demonstrated in mild-to-moderate asthma, and fewer exacerbations requiring oral corticosteroids were experienced.73 Zileuton suppresses exercise-induced bronchoconstriction74 as well as that due to aspirin in sensitive individuals.75 It has been associated with elevated liver enzymes and reports of reversible hepatitis and hyperbilirubinemia. Monitoring of liver function tests prior to initiating therapy and periodically is recommended. Zileuton is hepatically metabolized and affects the CYP3A4 microsomal isoenzymes, and can result in elevated terfenadine (withdrawn from U.S. market in 1998) and theophylline levels. As of 2008, zileuton, is available only as an extended release tablet and should be taken within the hour following the morning and evening meals.

Anticholinergics

Inhaled anticholinergics are FDA approved for the treatment of bronchospasm associated with COPD. They offer an alternative to patients that are intolerant of beta2-agonists and are the treatment of choice for bronchoconstriction caused by beta-blocker medication. Inhaled anticholinergics are classified as quick-relief drugs that may have additive effects to beta2-agonists but with a slower onset of action. Ipratropium, tiotropium and oxtiropium (not currently available in the U.S.) are quaternary compounds related to atropine. They are preferred over atropine in that they have minimal systemic absorption and consequently fewer related side effects. Tiotropium bromide, a long acting inhaled anticholinergic agent, has not been studied in the long-term management of asthma and thus does not have FDA approval for use in the disease. It is indicated for once daily therapy in the treatment of COPD.

Airway smooth muscle tone is regulated by both sympathetic and parasympathetic innervation. Anticholinergics affect only cholinergically mediated parasympathetic bronchoconstriction. Parasympathetic activity is blocked by competitive, non-selective inhibition of muscarinic cholinergic receptors. Acetylcholine is prevented from stimulating guanylyl cyclase, which results in reduced formation of cyclic guanosine monophosphate (cGMP) a mediator of bronchoconstriction. Bronchoconstriction resulting from neural reflex activation of cholinergic pathways is also blocked and mucus gland secretion may be decreased by anticholinergic agents.

Ipratropium and tiotropium are effective bronchodilators in patients with COPD but less so in chronic asthma.76 Nebulized ipratropium bromide proved almost as effective as beta2-agonists in the treatment of acute severe asthma.77

Aerosol Delivery Devices

The benefits from the inhaled pharmacologic treatments for asthma depend upon proficient use of aerosol delivery devices. Health care professionals should become knowledgeable of proper device use, and then seize every opportunity to educate and evaluate patient technique.

Metered-dose inhaler (MDI) delivery devices are used to provide inhaled beta2-agonists, corticosteroids, cromolyn sodium, nedocromil and anticholinergic medications. They can generally be used by patients greater than 5 years of age. After removing the cap and shaking the inhaler, it is held upright and positioned either 1-2 inches from the opened mouth or in the mouth (not recommended for corticosteroids). With the head tilted slightly back the user exhales then breathes in evenly and deeply over 3-5 seconds through the mouth, activating the inhaler at the start of inhalation. The inhalation should be held for 10 seconds to allow the medicine to reach deep into the lungs. Repeat doses are performed allowing 1 minute between puffs. With this method, up to 80 percent of the actuated dose is
deposited in the oropharynx. Mouth rinsing can reduce systemic absorption from these deposits. Some beta<sub>2</sub>-agonists are available in breath-actuated metered dose inhalers. These are useful in individuals unable to coordinate inhalation and actuation. A disadvantage is that the force of inhalation required for actuation is greater than what is desired to avoid drug deposit in the oropharynx. Many MDIs, until recently, contained chlorofluorocarbons (CFCs) as propellants; CFCs have been found to deplete ozone and have been banned internationally. MDIs with other propellants, such as the nonchlorinated propellant HFA 134a, and other devices, are being introduced.

**Dry powder inhalers (DPIs)** require a different inhalation technique. The mouth must be closed tightly around the mouthpiece and inhalation performed rapidly and deeply over 1-2 seconds.

**Spacer ‐valved holding chamber devices** are particularly useful for young children and anyone using inhaled corticosteroids. A facemask may be attached for use in children less than 4 years of age. Inhalation is slow over 3-5 seconds or with tidal breathing immediately after inhaler actuation into chamber. The inhaler is actuated only once per inhalation. If a facemask is used, 3-5 inhalations are advised for each actuation. Spacer/valved holding chambers are easier to use than MDIs alone and decrease oropharyngeal deposit and subsequent systemic absorption of inhaled drugs. Beta<sub>2</sub>-agonists, cromolyn, anticholinergics and corticosteroids may be delivered via a nebulizer apparatus. This method is appropriate in the very young and any patient unable to use an MDI with spacer/valved holding chamber or spacer and facemask (e.g., during exacerbations), as it is less dependent on patient coordination or cooperation. Drawbacks are that the machines are expensive, bulky, and time consuming to operate.

**PHARMACOLOGIC THERAPY: MANAGING ASTHMA LONG-TERM**

The overall long-term goal for therapy is to control asthma reducing impairment and risk. The pharmacologic management of asthma should meet the goals of therapy by maintaining control with minimal adverse drug effects. This can be accomplished, in part, by tailoring therapy so that only the least amount of medication necessary is used.

The Expert Panel has offered recommendations for the treatment of asthma. These are summarized in Table 5. They are arranged in steps according to asthma severity and are intended to be used as general guidelines. In the stepwise approach, the dose and number of medications and administration frequency are increased as necessary and decreased when possible to achieve and maintain control of the disease. Expert Panel-3 has expanded the stepwise approach to managing asthma to six steps of care. Specific therapy should be tailored to the needs and circumstances of individual patients. Patient education and measures to minimize factors which contribute to their asthma must be included. The stepwise approach for managing asthma provides an organized method for altering drug therapy to achieve, and then maintain control. It addresses the chronic, inflammatory nature of asthma, and the need to suppress inflammation and prevent exacerbations over the long-term.

Therapy may be initiated in a variety of ways. The Expert Panel describes two stepwise approaches based on the classification of asthma severity as previously discussed. Treatment can begin at the step appropriate for the level of patient severity or at a higher level for a more aggressive approach to control.

Adjustments upward can be made gradually with the first method if needed or downward with the second once control is obtained. The Panel prefers the later because symptoms and altered pulmonary function are related to airway inflammation, which is more effectively suppressed with higher corticosteroid doses. Once asthma is controlled, clinical benefits can be retained with lower doses. The object of this approach is to rapidly suppress inflammation, then restore and maintain pulmonary function with possibly a lower total steroid requirement.

Monitoring is a vital component of treatment. The factors indicating control must be continuously evaluated so that therapy can be appropriately adjusted. Monitor at two and six week intervals when therapy is initiated to evaluate asthma control. Follow up visits, which the Panel suggests at 1 to 6 month intervals, are essential. Several considerations should be addressed prior to adjusting therapy in the event the patient’s asthma is not controlled. Compliance with their medication regimen in addition to technique of administration and monitoring should be assessed.

The Expert Panel recommends a detailed, written asthma action plan for all patients with guidelines for acute interventions for exacerbations. Changes in environment with new or greater exposure to allergens or irritants may be responsible. Psychosocial problems or family barriers to adequate self-management may be interfering with their control. Contributing conditions, such as sinusitis, or review of diagnosis should also be evaluated. If indicated, an increase to the next higher step of care may be necessary. In some, a temporary increase in anti-inflammatory therapy, such as a short course of oral prednisone, may accomplish control. Note that a rescue course of systemic corticosteroids may be needed at any time and at any step. This is particularly true in some patients with intermittent asthma who experience severe and life-threatening exacerbations separated by long periods of normal lung function and no
symptoms. Consultation with an asthma specialist may be required.

Once control has been demonstrated for several weeks or months, a step-down or reduction in pharmacologic support should be undertaken. This will help establish the minimum medication requirement to maintain control. Decreases in therapy should be made gradually due to the variable rate and intensity in which asthma can deteriorate.

Generally, the last medication added should be the first to be reduced. Rigid guidelines for medication reductions don’t exist, but it is the Panel’s opinion that inhaled corticosteroids may be reduced by 25 percent every 2 to 3 months until the lowest dose maintaining control is reached. Patients with persistent asthma will most likely need continuous use of inhaled steroids as relapse may occur if completely stopped. 78

### Table 5. STEPWISE APPROACH FOR MANAGING ASTHMA IN PATIENTS > TO 12 YEARS OF AGE AND ADULTS

<table>
<thead>
<tr>
<th>STEP 6</th>
<th>Severe Persistent asthma</th>
<th>Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High-dose ICS + LAB + oral corticosteroids AND Consider omalizumab for patients who have allergies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 5</th>
<th>Severe Persistent asthma</th>
<th>Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-High-dose ICS + LABA AND Consider omalizumab for patients who have allergies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 4</th>
<th>Moderate Persistent asthma</th>
<th>Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-Medium-dose ICS + LABA</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Alternative:</strong> -Medium-dose ICS and either leukotriene receptor antagonist, theophylline or zileuton</td>
</tr>
</tbody>
</table>

**Education:** for step 4 and above, include steps 2 & 3 plus refer to individual education/counseling

<table>
<thead>
<tr>
<th>STEP 3</th>
<th>Moderate Persistent asthma</th>
<th>Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-Low-dose ICS + LABA OR -Medium-dose ICS <strong>Alternative:</strong> -Low dose ICS + either leukotriene receptor antagonist, theophylline or zileuton</td>
</tr>
</tbody>
</table>

**Education:** Step 1 actions plus: - Refer to group education if available
- Review and update

<table>
<thead>
<tr>
<th>STEP 2</th>
<th>Mild Persistent asthma</th>
<th>Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-Low-dose ICS <strong>Alternative:</strong> -cromolyn, leukotriene receptor antagonist, nedocromil, OR theophylline</td>
</tr>
</tbody>
</table>

**Education:** Step 1 actions plus: - Refer to group education if available
- Review and update
- Teach self-monitoring

### Long-Term Control Daily Medications Required for Steps 2 and above

**Preferred:** SABA as needed

**Education:**
- Teach basic facts about asthma
- Teach inhaler, spacer, holding chamber technique
- Discuss roles of medications
- Develop self-management plan

- Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations
- Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants

### Quick Relief
- Short-acting bronchodilator: 2-4 puffs short-acting inhaled beta₂-agonists as needed for symptoms.
- Intensity of treatment will depend on severity of symptoms; 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.

### Step Down:
- Review treatment every 1-6 months; if asthma is well controlled for at least 3 months, a gradual stepwise reduction in treatment may be possible.

### Step Up:
- If control is not maintained, consider step up 1 step. Review patient medication technique, adherence, environmental control and comorbid conditions. Reevaluate in 2-6 weeks. For very poorly controlled asthma, consider short course of oral systemic corticosteroids and step up 1-2 steps; reevaluate in 2 weeks.
**INTERMITTENT ASTHMA: STEP I**

Daily medications are not needed for intermittent asthma. Periodic use of a short acting inhaled beta₂-agonists is generally sufficient to relieve symptoms and improve pulmonary function. If symptoms reoccur or the inhaled SABA is required more than two times a week, not including use for exercise-induced bronchospasm (EIB), the patient should be treated for persistent asthma.

**PERSISTENT ASTHMA**

Daily long-term control is indicated in all steps of persistent asthma. Since asthma is a chronic inflammatory disorder with reoccurring exacerbations, therapy for persistent asthma must suppress inflammation over the long-term and prevent exacerbations.

Quick relief medication must be available for all patients with persistent asthma. Increasing use of a SABA or use more than 2 days a week for symptom control indicates the need to step up therapy.

Patients with seasonal allergies, i.e. those with asthma symptoms only in relation to certain seasonal molds or pollens, should be treated as having persistent asthma during the season and as having intermittent asthma the rest of the year.

**MILD PERSISTENT ASTHMA: STEP 2**

In mild persistent asthma low dose inhaled corticosteroids are preferred as daily anti-inflammatory therapy. Cromolyn or nedocromil, leukotriene modifiers or sustained release theophylline are acceptable alternatives for patients who have mild persistent asthma. In accordance with the 2007 revised guidelines low-dose ICS have been designated the preferred treatment in children as well. Table 6 lists estimated comparative daily dosages for ICS. ICS are the most potent inhaled anti-inflammatory agents currently available. It should be emphasized that their use can improve asthma control, normalize lung function, and possibly prevent irreversible airway injury.

Sustained-release theophylline is an optional long-term control medication. Advantages are that it is relatively inexpensive and can be taken once or twice daily in an

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
<td>Child*</td>
<td>Adult</td>
</tr>
<tr>
<td>Beclomethasone HFA MDI</td>
<td>80-240 mcg</td>
<td>&gt;240-480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td>80-160 mcg</td>
<td>&gt;160-320 mcg</td>
<td></td>
</tr>
<tr>
<td>Budesonide DPI 90 or 180 mcg/inhalation</td>
<td>180-600 mcg</td>
<td>&gt;600-1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>Inhalation suspension for nebulization</td>
<td>0.5 mg</td>
<td>1.0 mg</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>Flunisolide MDI 250 mcg/puff</td>
<td>500-1,000 mcg</td>
<td>&gt;1,000-2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA MDI 80mcg/puff</td>
<td>320 mcg</td>
<td>&gt;320-640 mcg</td>
<td>&gt;640 mcg</td>
</tr>
<tr>
<td>Fluticasone MDI: 44,110, or 220 mcg/puff</td>
<td>88-264 mcg</td>
<td>&gt;264-440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>100-300 mcg</td>
<td>&gt;300-500 mcg</td>
<td>&gt;500 mcg</td>
</tr>
<tr>
<td>Mometasone DPI 200 mcg/puff</td>
<td>200 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetonide MDI</td>
<td>300-750 mcg</td>
<td>&gt;750-1500 mcg</td>
<td>&gt;1500 mcg</td>
</tr>
<tr>
<td>75 mcg/puff</td>
<td>300-600 mcg</td>
<td>&gt;600-900 mcg</td>
<td></td>
</tr>
</tbody>
</table>

*Child: 5-11 years of age; Adult: ≥ 12 years of age; HFA = hydrofluoralkane

- The most important determinant of appropriate dosing is the clinician’s judgment of the patient’s response to therapy. The clinician must monitor the patient’s response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- Some dosages may be outside package labeling.
- Metered-dose inhaler (MDI) dosages are expressed as the actuator dose (the amount of drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, all of which is not available to the patient), which is used in many European countries and in some of the scientific literature. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation.
oral form. However, it is not preferred due to several disadvantages. Its pharmacologic effects are primarily bronchodilatory with mild desired anti-inflammatory action. Multiple factors influence drug clearance resulting in significant inter-patient variability in doses necessary to maintain serum levels of 5-15 mcg/mL. Consequently, serum monitoring of theophylline levels is necessary.

Leukotriene attenuators are alternative long-term control drugs. Zafirlukast can be used for patients 5 years and older, montelukast in those as young as 12 months of age, and zileuton in those 12 years and older. They can be considered when oral therapy is preferred.

Inhaled short-acting beta\(_2\)-agonists should be available for use as quick-relief medication as need to relieve symptoms. Up to two treatments of 2-6 puffs via a metered dose inhaler (MDI) at 20-minute intervals or a single nebulizer treatment is suggested for initial treatment.

**MODERATE PERSISTENT ASTHMA: STEPS 3 & 4**

Due to the complexity of managing medications and asthma at this level, consultation with an asthma specialist may be beneficial. Two equally acceptable treatment options are recommended by EPR-3. (1) The preferred treatment for adults and children over 5 years of age is to add a long-acting inhaled beta\(_2\)-agonist (salmeterol or formoterol) to a low dose of inhaled corticosteroid. This combination is best, as demonstrated by the available clinical trials, for disease control and at decreasing the number of asthma episodes. However, as previously mentioned, LABAs may increase the severity of asthma episodes and chance of death when they do occur. (2) The alternative treatment option is to continue the inhaled corticosteroid and increase the dose to the medium dose range.

Additional alternative therapy options couple low-dose inhaled corticosteroids with either a leukotriene modifier or theophylline. While apparently beneficial, evidence for using these combinations is lacking. If symptoms require, the inhaled corticosteroids may be increased to the medium-dose range for this treatment step. Two preferred treatment options are given for children younger than 5 years of age: LABA with a low dose ICS or medium-dose ICS alone. Inhaled SABA are used as previously described for quick-relief of symptoms in acute exacerbations.

The preferred Step 4 treatment for severe persistent asthma is to increase the dose of the ICS to the medium-dose range and add a LABA. This is recommended for patients who are not well controlled by Step 3 therapy, those experiencing severe exacerbations requiring oral systemic corticosteroids, visits to emergency rooms or admission to hospital. Alternatives to Step 4 therapy include medium dose ICS combined with a leukotriene receptor antagonist, theophylline or zileuton.

**SEVERE PERSISTENT ASTHMA: STEPS 5 & 6**

High doses of inhaled corticosteroids and long-acting bronchodilators are the preferred treatment for patients with severe persistent asthma. Frequently, oral systemic corticosteroids on a regularly scheduled, long-term basis are also required as in Step 6. Adverse effects attributed to corticosteroids are likely, so once controlled, attempts should be made to reduce the systemic steroid to the smallest dose necessary. Alternate day therapy may produce less adrenal suppression. Omalizumab may be considered for patients in Steps 5 and 6 care, who have sensitivity to certain allergens.

**SPECIAL CONSIDERATIONS FOR DIFFERENT AGE GROUPS**

**INFANTS AND CHILDREN 4 YEARS AND UNDER**

Diagnosis is difficult in this age group and may be assisted with a therapeutic trial of asthma medication. Cough and wheeze are more frequently labeled as chronic bronchitis, wheezy bronchitis, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infection rather than asthma. Consequently, those with asthma may not be receiving appropriate long-term control medications.

Expert Panel-3 states that the goal of asthma therapy in children is to maintain control of asthma with the least amount of medication and therefore minimal risk of adverse effects. Specifically, to prevent coughing and breathlessness in the daytime, at night and after exercise; to maintain near normal lung function; to require ≤ 2 days a week administration of SABA for quick relief of symptoms; to maintain normal activity levels; and to prevent recurrent exacerbations of asthma and need for emergency visits to doctor and hospital.4

Long-term anti-inflammatory therapy should be considered if treatment for symptomatic relief is required more than two times per week. The effects of persistent uncontrolled asthma must be weighed against potential adverse effects from long-term medication use. ICS are effective in long-term clinical studies with infants79 and cromolyn and nedocromil reduce symptoms and airway hyperresponsiveness.80,81 Low dose ICS are the preferred daily long-term control therapy.
Other considerations include:
- Patient Education and Environmental Control essential at each step.
- SABA as need for quick relief of symptoms. Up to 3 treatments at 20-minute intervals as needed.
- With viral respiratory infection: SABA every 4-6 hours up to 24 hours or longer with physician consult. Consider short course of systemic steroids if exacerbation is severe or patient has history of previous severe exacerbations.
- Frequent use of SABA may indicate the need for step up treatment.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment stepping up.
- ICS approved for use in children 0-4 years of age: budesonide inhaled suspension for nebulization and fluticasone HFA/MDI.

Monitoring is essential to directing subsequent changes in therapy. If no clear benefits are observed, treatment should be stopped and alternative therapies tried or the diagnosis reevaluated.

**SCHOOL-AGE CHILDREN/ADOLESCENTS: AGES 5-11**

EPR-3 added the 5-11 age guidelines as the result of new evidence on medication treatment for this age group.

Special consideration is warranted with regards to school and social development for this age group. Adolescents should participate actively in the construction of their asthma management plans. Educational software in the form of a computer game has offered promising results in educating children in inhaler technique and knowledge of asthma. Compliance can be diminished by their failure to understand the complications of uncontrolled asthma, denial of chronic illness, or perceptions of lost independence. Education and inclusion of their involvement in treatment plans should address adolescent developmental issues such as self-image, confidence, responsibility, and problem solving abilities.

A written asthma management plan from the clinician should be provided for the student’s school. It should include a plan for handling exacerbations, instructions for long-term control medications, and where appropriate, prevention of exercise-induced bronchospasm. This information must be in agreement with existing school policies and school nurse coverage. Full participation in physical activities should be encouraged. Excessive fatigue from play or exercise may signal the need for a step up in long-term therapy.

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**TABLE 7: Pharmacologic Steps for Management of Childhood Asthma**

<table>
<thead>
<tr>
<th>STEP</th>
<th>Children 0-4 Years of Age</th>
<th>Children 5-11 Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Intermittent Asthma</td>
<td>SABA as needed</td>
<td>SABA as needed</td>
</tr>
<tr>
<td>2: Mild Persistent Asthma</td>
<td>Preferred: low-dose ICS. Alternative: cromolyn or montelukast SABA as needed</td>
<td>Preferred: low-dose ICS. Alternative: cromolyn, leukotriene receptor antagonist, nedocromil, or theophylline SABA as needed</td>
</tr>
<tr>
<td>3: Moderate Persistent Asthma</td>
<td>Preferred: medium-dose ICS SABA as needed</td>
<td>Preferred: medium-dose ICS. Alternative: medium-dose ICS AND either leukotriene receptor antagonist or theophylline SABA as needed</td>
</tr>
<tr>
<td>4: Moderate Persistent Asthma</td>
<td>Preferred: medium-dose ICS + either LABA or montelukast SABA as needed</td>
<td>Preferred: medium-dose ICS + LABA. Alternative: medium-dose ICS AND either leukotriene receptor antagonist or theophylline SABA as needed</td>
</tr>
<tr>
<td>5: Severe Persistent Asthma</td>
<td>Preferred: high-dose ICS AND either LABA or montelukast SABA as needed</td>
<td>Preferred: high-dose ICS AND LABA. Alternative: high-dose ICS AND either LTRA or theophylline SABA as needed</td>
</tr>
<tr>
<td>6: Severe Persistent Asthma</td>
<td>Preferred: high-dose ICS AND either LABA or montelukast + oral systemic corticosteroids SABA as needed</td>
<td>Preferred: high-dose ICS + LABA + oral systemic corticosteroids. Alternative: high-dose ICS + either leukotriene receptor antagonist or theophylline + oral systemic corticosteroids SABA as needed</td>
</tr>
</tbody>
</table>

**Persistent asthma** requires daily long-term control for children who have four or more wheezing episodes in one year and risk factors for persistent asthma. Quick relief medications must be available and taken as needed to relieve symptoms.
OLDER ADULTS
Older adults are likely to have other obstructive lung diseases such as chronic bronchitis or emphysema. A two to three week trial of systemic corticosteroid therapy can be useful to determine reversibility of the airway disease. Tolerance of asthma medications may diminish with age and the potential for interaction with other disease processes and treatments increases.

MANAGING SPECIAL SITUATIONS IN ASTHMA

SEASONAL ASTHMA
The step-wise approach to treating seasonal asthma caused by exposure of certain pollens and molds is recommended. If occurrence is predictable, daily long-term anti-inflammatory therapy can begin prior to the season start and continued throughout.

COUGH VARIANT ASTHMA
Diagnosis of cough variant asthma can be difficult. It occurs primarily in young children and is commonly associated with nocturnal coughing. Daytime examinations may appear normal. Morning and afternoon PEF monitoring and/or a trial of anti-inflammatory or bronchodilator medication may be required for diagnosis. Treatment follows the step-wise approach.

EXERCISE-INDUCED BRONCHOSPASM
Exercise-induced bronchospasm (EIB) should be anticipated in all asthmatics. It is caused by a loss of heat, water, or both from the lung brought about by hyperventilation from exercise. Symptoms, such as shortness of breath, chest pain or tightness, wheezing, or poor endurance, typically occur during or minutes after vigorous activity and peak 5 to 10 minutes after stopping the activity. A 15 percent reduction in PEF or FEV1, with measurements taken before and after exercise at 5 minute intervals, for 20-30 minutes, is consistent with EIB. Bronchospasm generally subsides after 20-30 minutes. Patients with no other symptoms should be evaluated periodically as EIB is a marker of uncontrolled asthma.

An important goal of treatment in EIB, as with all asthma, is to enable patients to fully participate in any activity they wish free of symptoms. For some, an extended warm-up period prior to exercise may minimize symptoms. Others will benefit from pre-activity pharmacologic treatment. Beta2-agonists prevent symptoms in greater than 80 percent of patients. Short-acting inhaled beta2-agonists are effective for 2 to 3 hours when used just before activity. Long-acting salmeterol can prevent EIB for 10 to 12 hours but should be used 30 to 60 minutes before exercise due to its slower onset of action. The cromones, cromolyn and nedocromil, used prior to exercise also prevent EIB. Communication with teachers, coaches, and trainers, is necessary regarding the need for medication before exercise. Those in competitive sports must be knowledgeable of and conform to the governing organization’s regulations regarding drug use. The United States Olympic Committee (USOC) 1-800-233-0393, International Olympic Committee (IOC) and National Collegiate Athletic Association (NCAA) are some organizations with rules pertaining to drug use and competition.

SURGERY AND ASTHMA
Asthma patients may be at increased risk for complications during and after surgery due to preexisting airway hyperresponsiveness, airflow obstruction, mucus hypersecretion, and latex sensitivity. These conditions make them more apt to experience bronchoconstriction triggered by intubation, hypoxemia and possible hypercapnia, impaired effectiveness of cough, atelectasis and respiratory infection, and reaction to latex.

Surgical candidates with asthma should be carefully evaluated for symptoms, medication use, and pulmonary function. Attempts to improve pulmonary function to predicted values or the patient’s personal best should be attempted prior to surgery. A short course of systemic corticosteroids may accomplish this. Patients with systemic corticosteroid use during the previous 6 months should be given systemic hydrocortisone 100 mg every 8 hours during the surgical period and reduced quickly in the subsequent 24 hours. This protects against adrenal insufficiency during a period of stress in individuals with possible adrenal axis suppression.

PREGNANCY AND ASTHMA
Reportedly, approximately 3-8% of pregnant women are affected by asthma. The control of this condition is important in pregnancy and its lack can influence pre-eclampsia, perinatal mortality, prematurity and low birth weight. Many asthma drugs pose little risk to the fetus while others such as decongestants (except pseudoephedrine), antibiotics (tetracycline, sulfonamides, and fluoroquinolones), live virus vaccines, immunotherapy (if doses are increased), and iodides have possible risks.

The Quick Reference from the Working Group on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment (Update 2004), recommends treating the pregnant patient with asthma medications to prevent symptoms and exacerbations. The Group reports that inadequate maternal asthma
control is a greater risk to the fetus than the use of medications. They also promote a collaborative team approach that involves many of the key care providers such as obstetrics, anesthesia, pulmonology, and neonatology. Although there are no studies that directly test the effectiveness of asthma medications in the pregnant woman, the Group’s assumptions are that they are the same as those in the non-pregnant woman.

The Group’s recommendations made in the 2004 update are:

- Asthma status should be monitored during prenatal visits; asthma improves in one-third of women and worsens in approximately one-third during pregnancy.
- Albuterol is the preferred short acting beta2-agonist based on its safety profile during pregnancy.
- Inhaled corticosteroids are the preferred long-term asthma control medication.
- Intranasal corticosteroids are recommended for the treatment of allergic rhinitis; as well as second-generation antihistamines (loratidine or cetirizine).

For more in depth information, refer to the NAEPP Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment-Update 2004 (NIH Publication No. 05-5236).

**STRESS AND ASTHMA**

Stress appears to trigger asthma exacerbations in some and may be a risk factor for an increase in asthma prevalence. Enhanced pro-inflammatory cytokines may partially explain this phenomenon. Psychosocial factors interfering with care and leading to poor outcomes are also important. The four components of management are similar to those for any patient with asthma with considerations made regarding the progression of the pregnancy and fetal activity (Figure 2):

- Monthly assessment and monitoring of asthma, including objective measures of pulmonary function
- Control of factors that contribute to the severity of asthma
- Patient education
- The stepwise approach to pharmacologic therapy

---

**Figure 2. MANAGEMENT OF ASTHMA EXACERBATIONS (Pregnancy considerations in italics): HOME TREATMENT**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Measure PEF: Value &lt; 50% personal best or predicted, suggests severe exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOTE: Signs and symptoms: Degrees of cough, breathlessness, wheeze, and chest tightness correlate imperfectly with severity of exacerbation</td>
</tr>
<tr>
<td></td>
<td>Accessory muscle use and suprasternal retractions suggest severe exacerbation.</td>
</tr>
<tr>
<td>FOR PREGNANCY</td>
<td>Note presence of fetal activity*</td>
</tr>
</tbody>
</table>

**Initial Treatment**

Inhaled short-acting beta2-agonist: Up to 2 treatments of 2-6 puffs by MDI at 20-minute intervals or nebulizer treatments

**Good Response**

- Mild Exacerbation
  - PEF > 80% predicted or personal best
  - No wheezing or shortness of breath
  - Response to beta2-agonist sustained for 4 hours
  - Appropriate fetal activity*
  - May continue beta2-agonist every 3-4 hrs for 24-48 hrs
  - Consider short course of oral corticosteroids

  Contact clinician for follow-up instructions

**Incomplete Response**

- Moderate Exacerbation
  - PEF 50 - 79% predicted or personal best
  - Persistent wheezing or shortness of breath
  - Decreased fetal activity*
  - Add oral corticosteroid
  - Continue beta2-agonist

  Contact clinician urgently (this day) for instructions Proceed to emergency department

**Poor Response**

- Severe Exacerbation
  - PEF < 50% predicted or personal best
  - Marked wheezing, or shortness of breath
  - Decreased fetal activity*
  - Add oral corticosteroid
  - Repeat beta2-agonist immediately
  - If distress is severe and non-responsive, call your doctor and proceed to emergency department, consider calling 911

Proceed to emergency department

*Fetal activity is monitored by observing whether fetal kick counts decrease over time. NOTE: Patients at high risk of asthma related deaths should receive immediate clinical attention after initial treatment. Additional therapy may be required.*
Pharmacologic Therapy: Managing Exacerbations of Asthma

Asthma exacerbations are episodes of worsening symptoms and decreasing pulmonary function that impair one’s ability to conduct their usual activities. Respiratory viral infections are the most common cause but other triggers include exposure to allergens, irritating substances, air pollution, and some medications (e.g. beta-blockers, aspirin sensitivity). Reduction of long-term control medications beyond that necessary to maintain control may also be responsible. Emotional extremes may also initiate exacerbation.

Early treatment is important to correct significant hypoxemia, reverse airflow obstruction, and reduce the likelihood of recurrence. Key components to achieving this are a written action plan, early recognition of indicators, appropriate communication between patient and clinician, and removal of precipitants contributing to the exacerbation.

A written action plan guides patient self-management and should be individualized as to setting (e.g. school, home, work), severity, and patient/care giver capability (Figure 2). These are most important for those with moderate-to-severe persistent asthma or a history of severe exacerbations. The plan should offer specific treatments for particular signs, symptoms, and peak flow measurements, as well as how, when, and where to seek medical help. Medications and equipment to administer them and monitor their effects must be available. Early exacerbation recognition is supported by patient monitoring and education. Objective measures such as spirometry or peak expiratory flow more reliably indicate severity of exacerbations than do assessment of symptoms. Pulmonary function measurements are crucial for early recognition in patients unable to sense early airway narrowing.

Inhaled SABA, in repeated doses if necessary, are utilized to initiate treatment for asthma exacerbations. Systemic corticosteroids are indicated in patients with moderate-to-severe exacerbations or those unresponsive to inhaled beta2-agonists. In patients on inhaled corticosteroids experiencing a mild exacerbation, the dose may be doubled until peak flow returns to predicted or personal best. The added or increased steroid therapy should be continued until symptoms and PEF are stable which may require several days. Patients need to understand what constitutes excessive or prolonged bronchodilator therapy and should be instructed to seek medical care if improvement is not rapid and sustained or the exacerbation is severe.

Table 8. Risk Factors for Death from Asthma

- Past history of sudden severe exacerbations
- Prior intubation for asthma
- Prior admission for asthma to an intensive care unit
- Two or more hospitalizations for asthma in the past year
- Three or more emergency care visits for asthma in the past year
- Hospitalization or an emergency care visit for asthma within the past month
- Use of > 2 canisters per month of inhaled short-acting beta2-agonist
- Current use of systemic corticosteroids or recent withdrawal from systemic corticosteroids
- Difficulty perceiving airflow obstruction or its severity
- Co-morbidity, as from cardiovascular diseases or chronic obstructive pulmonary disease
- Serious psychiatric disease or psychosocial problems
- Low socioeconomic status and urban residence
- Illicit drug use
- Sensitivity to Alternaria (fungi)

Thorough education, monitoring, and care are warranted for those with risk factors for death from asthma (Table 8). They should be counseled to seek medical care early. Infants with asthma are at greater risk for respiratory failure and should be managed accordingly (Table 9).

In the event of severe exacerbations, short-acting bronchodilators and supplemental oxygen administration should begin as early as feasible (Drs. office, ambulance). These episodes will generally require close observation for deterioration, frequent treatments, and repetitive measurement of lung function, which can be provided best at an emergency department.

Table 9. Special Considerations for Infants

- Assessment depends on physical examination rather than objective measurements. Use of accessory muscles, paradoxical breathing, inspiratory and expiratory wheezing, cyanosis, and a respiratory rate > 60 are key signs of serious distress
- Objective measurements such as oxygen saturation of < 91 % also indicate serious distress.
- Response to beta2-agonist therapy can be variable and may not be a reliable predictor of satisfactory outcome. However, because infants are at greater risk for respiratory failure, a lack of response noted by either physical examination or objective measurements should be an indication for hospitalization.
- Use of oral corticosteroids early in the episode is essential but should not substitute for careful assessment by a physician.
- Most acute wheezing episodes result from viral infections and may be accompanied by fever. Antibiotics are generally not required.
EMERGENCY DEPARTMENT AND HOSPITAL MANAGEMENT OF ASTHMA EXACERBATIONS

In the emergency department, treatment should begin as soon as an asthma exacerbation is recognized and an assessment of lung function is made. Objective information (FEV₁ or PEF) is useful in determining severity of airflow obstruction and response to treatment. Figure 2 classifies asthma exacerbation severity according to symptoms and pulmonary function.

Once underway, a brief history is obtained and a physical examination pertinent to the exacerbation is performed to determine severity and subsequent treatment. The history should reveal time of exacerbation onset, cause, and current medications, including the time of last doses. Information regarding previous exacerbations such as symptom severity relative to the current episode, prior hospitalizations, emergency department visits, and other potentially complicating illness should be determined. Physical examination evaluates indicators of severity, identifies complications (e.g., pneumonia, pneumothorax, or pneumomediastinum) or conditions that may affect asthma (e.g., allergic rhinitis, rhinitis, sinusitis), and rules out upper airway obstruction.

Laboratory studies may be conducted after initial treatment is underway. The most important objective is to identify actual or impending respiratory failure. Studies can be performed to identify theophylline toxicity and evaluate complicating conditions. Arterial blood gas (ABG) should be considered to measure arterial carbon dioxide tension (PCO₂) in those suspected of hypoventilation, severe distress, or with FEV₁ or PEF less than 25 percent of predicted after initial treatment. Respiratory drive is frequently increased in asthma exacerbations so a “normal” PCO₂ may actually indicate severe airflow obstruction in these patients. A complete blood count (CBC) in patients with fever or purulent sputum may further assess for possible infection. Leukocytosis is common with asthma exacerbations and 1 to 2 hours after corticosteroid administration and should be considered when evaluating an elevated white blood cell count. Serum electrolyte monitoring is especially important in patients with cardiovascular disease taking diuretics. Beta₂-agonists can transiently decrease serum potassium, magnesium, and phosphate levels.

Cardiopulmonary processes in suspect individuals, such as pneumothorax, pneumomediastinum, pneumonia, lobar atelectasis, and congestive heart failure can be evaluated by chest radiography. Patients older than 50 years of age and those with heart disease or chronic obstructive pulmonary disease warrant an electrocardiogram and continuous monitoring of cardiac rhythm.

Anatomical and physiologic differences in the lungs of infants make them more susceptible to respiratory failure. They have greater peripheral airway resistance, fewer collateral channels of ventilation, airway smooth muscle that extends further into the peripheral airways, less elastic recoil, and mechanical disadvantage of the diaphragm. Viral infections, particularly respiratory syncytial virus, commonly cause wheezing in infants. This results in airway edema and inflammation, which can lead, to air trapping and hyperinflation, atelectasis, tachypnea, and wheezing which can quickly progress to respiratory failure. Close monitoring of signs, symptoms, and pulmonary function is important in this patient population and should include oxygen saturation monitoring with pulse oximetry.

Supplemental oxygen, inhaled beta₂-agonists, and systemic corticosteroids compose the primary emergency department/hospital treatment of asthma exacerbations (Figure 2). Multiple doses of ipratropium bromide for emergency department patients who have severe exacerbations may be considered; it is not recommended during hospitalization. The Expert Panel recommends that oxygen be administered to maintain SaO₂ > 90 percent (> 95 percent in pregnant women and those with coexistent heart disease). Inhaled SABAs are the most effective means of reversing airflow obstruction and should be used in all patients. Systemic corticosteroids are used in patients with moderate-to-severe exacerbations, those who do not respond completely to initial beta₂-agonist therapy, and those requiring admission to the hospital. They favorably affect resolution of airflow obstruction and tendency to relapse. New data suggests that after the first two days of intravenous steroids in patients hospitalized with severe asthma that high-doses of ICS are as effective as systemic steroids. Inhaled anticholinergics may increase bronchodilation beyond that produced by beta₂-agonists in some patients with severe airflow obstruction.

Adjunct treatments, such as intravenous magnesium sulfate or heliox, may be considered in severe, life-threatening exacerbations that are unresponsive to traditional initial treatments. Magnesium sulfate may be considered in those patients whose exacerbations remain severe after one hour of intensive therapy. Intravenous magnesium sulfate, 2 grams in adults and 25-75 mg/kg up to 2 grams in children added to conventional therapy has been shown to reduce hospitalization rates in emergency departments. Heliox, a mixture of helium and oxygen, may be used in patients...
who have life-threatening exacerbations and for those patients whose exacerbations remain severe after one hour of intensive traditional therapy. Heliox driven-albuterol nebulization has been postulated to improve gas exchange in patients who have airway obstruction. Significant improvements in pulmonary function in children and in adults are mixed.4

Other pharmacologic therapy common to the treatment of asthma has minimal value in the management of exacerbations. Acutely, methylxanthines (theophylline, aminophylline) don’t appear to offer additional benefit to optimal inhaled beta2-agonist and may increase adverse effects. Serum theophylline levels should be determined in patients taking theophylline containing drugs to rule out toxicity. Antibiotics should be reserved for those with fever and purulent sputum (due to polymorphonuclear leukocytes), evidence of pneumonia, or suspected bacterial sinusitis. Mucolytics (e.g., acetylcysteine, potassium iodide) should be avoided as they may worsen cough or airflow obstruction.65 Sedatives should not be used in severely ill asthma patients because of their respiratory depressant effects.

Several factors will determine if hospitalization is necessary. Despite appropriate therapy, approximately 10-25 percent of emergency room patients with acute asthma will require hospitalization. The patient’s duration and severity of symptoms, degree of airflow obstruction, history of prior exacerbations, and current medication use may suggest the likely course and need for monitoring and intervention. Availability of medical care and medications or psychiatric or social problems may prevent continuation of the initiated efforts and favor relapse.

Some patients will fail to respond to therapy and are likely to encounter respiratory failure. This can be due to worsening airflow obstruction and/or respiratory muscle fatigue. Signs of impending respiratory failure include a declining mental clarity, apnea, progressive fatigue, and a PCO2 >42 mm Hg. These patients will require endotracheal intubation and co-management by clinicians experienced in ventilator management.

The decision to discharge the patient depends on their response to therapy, and in hospitalized patients, adequate stabilization on oral and inhaled medications. In general they should have minimal symptoms and a PEF or FEV1 that is 70 percent of predicted or personal best. Prior to discharge, patients should receive instruction on medications, inhaler use, self-assessment techniques (e.g., monitoring symptoms, peak flow), and an action plan for future exacerbations. Plans for continuation of care should be established.

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**EDUCATION FOR A PARTNERSHIP IN ASTHMA CARE**

Complex pharmacologic regimens, environmental control strategies, exacerbation detection and self-treatment, and communication with health care providers must be executed proficiently for effective asthma management. Education of the patient and caregiver or family is essential to accomplishing this. Through it, patients gain motivation, skill, and confidence to control their asthma.92 Asthma education has proven to be cost-effective and capable of reducing morbidity in patients of all ages, particularly in high-risk patients.93,94

The Expert Panel recommends that patient education begin at the time of diagnosis and be incorporated into all steps of asthma care. This should be initiated by the clinician, which will help to emphasize its importance and promote open communication. At this point a partnership between patient and health care providers should be established. Subsequently all members of the health care team involved with the patient should reinforce and expand this knowledge. A team approach involving communication and coordination in efforts to provide consistency is advocated. Competent health care professionals, knowledgeable of contemporary treatment practices, but not part of a "formal team", should not be discouraged from providing these services.

Patients with asthma should be taught key educational messages and have them reinforced by all health care team members at every opportunity. They should understand basic facts about asthma such as the differences between normal and asthmatic airways and what happens in an asthma attack. Long-term control medications should be distinguished from quick relief drugs. Their purpose and how they work should be understood. Skills in inhaler use, spacer/holding chamber use, and symptom monitoring, including peak flow use, must be taught, demonstrated by the patient, and continually evaluated and reinforced. Patients should be instructed how to recognize early signs of deterioration. Education on environmental control measures such as identifying and avoiding precipitants or exposures should be included.

The patient must be included in structuring the management strategy because their acceptance and willingness to participate are key to the success of the plan. This can be assisted by jointly developing treatment goals. In this process the patient’s perception of asthma and its management’s effect on their life can be incorporated to personalize and give a sense of ownership.
An active partnership can be encouraged by providing a written plan for daily self-management of asthma, and management of exacerbations. The mutually agreed treatment goals are a logical part of these. Adjust the plans as needed and check to see that they are completely understood by the patient.

REFERENCES


70. Speciotor SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of IC204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. Am J Respir Crit Care Med. 1994;150:618-23.


POSTTEST

Please circle the correct answer on the answer sheet provided.

1. Asthma prevalence is highest among ____.
   a. Children 5-17 years of age
   b. Women
   c. Men
   d. Adults 18-44 years of age

2. Death due to asthma is more frequent among ____.
   a. Infants and children under 5 years of age
   b. Children 5-17 years
   c. Men 18-44 years of age
   d. Women and those over the age of 65

3. Which of the following statements on airway inflammation in asthma is incorrect?
   a. Whether acute, subacute, or chronic inflammation is always a feature of asthma.
   b. Inflammation has not been observed in patients’ airways with mild or asymptomatic asthma.
   c. The inflammatory process results through the interaction of multiple cell types and mediators.
   d. Inflammation of the airways may result in some changes that are irreversible.

4. Asthma is a chronic inflammatory disorder of the airways involving ____.
   a. mast cells, eosinophils, epithelial cells, macrophages, and activated T cells
   b. cytokines and chemokines
   c. a and b
   d. none of the above

5. Inflammatory features of the airways include ____.
   a. edema from increased vascular permeability
   b. collagen deposits beneath the basement membrane
   c. denuded epithelial membrane
   d. all of the above

6. Airway inflammation contributes to ____.
   a. airway hyperresponsiveness
   b. airflow limitation
   c. disease chronicity
   d. all of the above

7. Airflow obstruction in asthma may be caused by ____.
   a. mediators with anticholinergic activity
   b. swollen airway walls and mucosal thickening
   c. smooth muscle contraction from histamine and leukotrienes
   d. b and c

8. Which of the following is compatible with the diagnosis of asthma?
   a. obstruction that is not reversible
   b. episodic symptoms of airflow obstruction
   c. monophasic wheeze heard loudest over the glottis
   d. none of the above

9. Symptoms that are not considered primary indicators of asthma include ____.
   a. wheeze on exhalation
   b. eczema, hay fever, or atopic diseases
   c. reversible airflow limitation
   d. cough that worsens at night

10. Physical examination findings associated with asthma include ____.
    a. atopic dermatitis
    b. mucosal swelling
    c. chest hyperexpansion, particularly in children
    d. all of the above

11. Which of the following statements relating to spirometry in asthma is incorrect?
    a. It is preferred over monitoring peak expiratory flow when diagnosing asthma.
    b. Spirometry is the preferred method for ongoing patient self-monitoring.
    c. It can be used to measure response to modifications in drug therapy.
    d. The Expert Panel recommends spirometry evaluation at least every 1 to 2 years in patients with asthma.

12. Evaluating the reversibility of airflow obstruction ____.
    a. is typically accomplished through the use of an inhaled short-acting bronchodilator
    b. may require a trial of oral corticosteroid
    c. should always include measurement of PEF
    d. a and b
13. The asthma severity classification is based on ___.
   a. the severity rather than frequency of exacerbations
   b. degree of impairment and risk for future problems
   c. the patient’s response to 6 months of drug therapy
   d. all of the above

14. Asthma severity classification ___.
   a. is used to direct treatment but not monitor disease status
   b. changed “mild intermittent” category to “intermittent” with EPR-3 to emphasize that these individuals may have severe exacerbations
   c. is assigned at the level where the majority of the clinical features reside
   d. is assigned at the time of diagnosis and does not change over time

15. A patient with nighttime symptoms 4 times a month, a PEF with 20-30% variability, and daily use of his inhaled short-acting β2-agonist should be assigned to which severity grade?
   a. mild intermittent
   b. mild persistent
   c. moderate persistent
   d. severe persistent

16. All the following are among the goals of asthma therapy except ___.
   a. prevent chronic and troublesome symptoms
   b. maintain (near) “normal” pulmonary function
   c. maintain activity levels, excluding exercise and participation in sports requiring vigorous activity
   d. meet patient’s expectations of and satisfaction with asthma care

17. Periodic assessment and monitoring of pulmonary function ___.
   a. include spirometry study and peak flow monitoring
   b. helps to identify if goals of therapy have been achieved
   c. may be of particular importance to those unable to perceive airflow obstruction
   d. all of the above

18. The personal best peak flow measurement is ___.
   a. the highest number measured over a 2-3 week period when their asthma is poorly controlled
   b. used as a specific patient’s reference value
   c. should increase by 20% after taking a β2-agonist
   d. none of the above

19. Part of the long-term management of asthma is to avoid or minimize exposure to substances or factors, which cause or worsen symptoms. Which of the related statements is incorrect?
   a. A child with a sensitivity to animal dander is not at an increased risk for developing asthma.
   b. Occupational irritants may be suspect when symptoms occur only at work.
   c. Inhaled household allergens may include mold, house-dust mites, and animal saliva.
   d. Inhalant sensitivity is a less important cause of asthma in adults than in children.

20. The Expert Panel recommends that ___.
   a. all asthma patients, regardless of severity, be evaluated by an allergy specialist
   b. all patients with persistent asthma requiring daily therapy be evaluated for contributing allergies
   c. all patients with allergies receive immunotherapy
   d. patients with seasonal asthma use inhaled steroids continuously

21. Influenza vaccinations ___.
   a. are recommended yearly for all patients with asthma
   b. reduce the frequency of asthma exacerbations
   c. reduce the severity of asthma exacerbations
   d. can reduce the risk for influenza complications in those with persistent asthma

22. Conditions that may cause or worsen asthma symptoms include ___.
   a. peptic ulcer disease
   b. gastroesophageal reflux
   c. viral respiratory infections
   d. b and c

23. Adult asthma patients at risk for severe and possibly fatal reactions from aspirin or other nonsteroidal anti-inflammatory (NSAID) medications are those with ___.
   a. diverticulitis and intestinal polyps
   b. eczema
   c. nasal polyps and a history of bronchoconstriction after taking aspirin or other NSAID
   d. thrombocytopenia
24. Pharmacologic management of asthma ___.
   a. requires long-term control and quick-relief medications for all asthma severity classifications
   b. involves long-term control drugs for those with persistent asthma
   c. includes quick-relief medications directed toward symptoms such as cough, wheezing or chest tightness
   d. b and c

25. Long-term control drug therapy is directed toward ___.
   a. episodic bronchial smooth muscle relaxation
   b. chronic airway inflammation and associated symptoms
   c. rapid symptom relief in asthma exacerbation
   d. none of the above

26. Inhaled corticosteroid use for the long-term management of asthma ___.
   a. improves control in children and adults better than other long-term control medication
   b. prevent exacerbations
   c. improves peak expiratory flow, spirometry
   d. all of the above

27. Which of the following statements about corticosteroids is false?
   a. Their action on dendritic cells is responsible for their beneficial effects in asthma.
   b. Systemic corticosteroids have a role in both long-term control and quick-relief treatments.
   c. Systemic side effects are much less likely with inhaled vs. systemic corticosteroids.
   d. Systemic corticosteroids can reduce the rate of relapse in moderate to severe exacerbations.

28. Systemic side effects from corticosteroids ___.
   a. are eliminated by using inhaled forms
   b. are more likely to occur from inhaled steroids with extensive first-pass hepatic metabolism
   c. can result from inhaled steroid that is swallowed and absorbed from the lung
   d. may include accelerated linear growth in children

29. Reflex cough and bronchospasm from inhaled corticosteroids can be reduced by ___.
   a. slower rates of inspiration
   b. spacer or holding chamber use
   c. pretreatment with an inhaled beta2-agonist
   d. all of the above

30. Strategies to minimize adverse systemic effects from corticosteroids include all but ___.
   a. the addition of another drug class for control rather than increasing steroid dose
   b. the use of inhaled, not systemic corticosteroids for long-term control
   c. supplementing calcium and vitamin D in appropriate older female patients
   d. substituting long-acting beta2-agonists for corticosteroids for long-term control

31. Cromolyn sodium and nedocromil sodium ___.
   a. do not have anti-inflammatory effects in asthma
   b. have significant adverse effects which limit their usefulness
   c. should be avoided in children
   d. can reduce asthma symptoms and the need for quick-relief medications

32. The Expert Panel concludes there is sufficient evidence to support considering ___ as adjunctive therapy for severe persistent asthma patients with allergies who are poorly controlled while using ICS and a LABA.
   a. IVIG
   b. cyclosporine
   c. omalizumab
   d. methotrexate

33. Long-acting beta2-agonists ___.
   a. can replace corticosteroids in long-term asthma control
   b. may worsen nocturnal symptoms
   c. include salmeterol (Serevent®) MDI and oral sustained release forms of albuterol
   d. are ineffective in preventing exercise-induced bronchospasm (EIB)

34. Which of the following statements on long-acting beta2-agonists is correct?
   a. LABAs are useful for nocturnal symptoms.
   b. Formoterol and salmeterol should not be used for acute asthma symptoms.
   c. LABAs are effective in preventing exercise-induced bronchospasm.
   d. all of the above

35. Short-acting beta2-agonist ___.
   a. oral forms are preferred over inhaled because they have a faster onset of action and fewer side effects
   b. continual use may promote the development of tolerance and diminish response
   c. use can indicate level of asthma control
   d. b and c
36. The methylxanthine class of drug therapy ___.
   a. is considered 1st line for long-term control of asthma
   b. is an option for long-term control when ICS and inhaled LABAs are too difficult to use
   c. produce their effect on airway smooth muscle by increasing intracellular levels of cAMP
   d. requires higher drug levels for immunomodulating or anti-inflammatory effects than for bronchodilation

37. Indicate which of the following statements about leukotriene modifiers is correct.
   a. All available drugs in this class can be taken without regard to meals or food.
   b. Zafirlukast, montelukast, and zileuton may cause liver dysfunction and require liver enzyme monitoring.
   c. These agents include leukotriene receptor antagonists and a 5-lipoxygenase inhibitor.
   d. Drugs in this class do not influence hepatic enzymes and consequently are not involved in related drug interactions.

38. A patient taking montelukast ___.
   a. might need more serum theophylline monitoring and dose adjustment due to its affect on metabolism
   b. must be 12 years or age or older
   c. might include a child with mild persistent asthma unwilling or unable to take inhaled corticosteroids
   d. should be advised to take it on an empty stomach for better absorption

39. Ipratropium is an inhaled anticholinergic that is ___.
   a. classified as a quick-relief medication
   b. effective in treating bronchoconstriction caused by beta-blocker medication
   c. preferred over atropine because of fewer systemic side effects
   d. all of the above

40. Which of the following statements on aerosol delivery devices is incorrect?
   a. Correct use of these devices will positively influence the benefits of inhaled pharmacologic treatments.
   b. MDI actuations should be inhaled rapidly to deposit drug particles further in the lower airways.
   c. DPIs are used with the mouth closed around the mouthpiece and rapid, deep inhalation with actuation.
   d. Nebulizers are appropriate for the very young or any person unable to use an MDI with a spacer/holding chamber or spacer and face mask.

41. An asthma patient with daily symptoms and a PEF with > 30% variability and 70% of predicted should receive ___.
   a. no daily medication
   b. daily inhaled corticosteroids, alone or in combination with a long-acting beta2-agonist
   c. education regarding basic asthma facts and avoidance of appropriate allergens
   d. b and c

42. The stepwise approach for managing asthma ___.
   a. provides an organized method to adjust drug therapy in asthma
   b. discourages the use of "bursts" or higher doses of steroids to gain asthma control
   c. mandates that therapy be started at a higher severity level, then tapered down
   d. requires no medication adjustments if symptoms are controlled

43. Once well controlled, a reduction in therapy may be possible. The Expert Panel ___.
   a. suggests a rapid weekly reduction in drug and/or dose once asthma
   b. recommends, when tapering therapy, to first reduce or delete the older drugs rather than new additions used to achieve disease control
   c. suggests a 25% reduction in ICS use every 2 to 3 months until the lowest controlling dose is achieved
   d. offers specific, rigid guidelines for reducing medications
44. Pharmacologic therapy for intermittent asthma (step 1) ____.
   a. includes daily low dose ICS
   b. is generally limited to intermittent use of a SABA
   c. is accomplished with periodic use of an ICS
   d. uses 3 day oral steroid courses for periodic symptoms

45. Long-term control medications are recommended ____.
   a. for all steps of asthma classified as persistent
   b. to suppress acute inflammatory responses
   c. year round use for asthma associated with seasonal allergies
   d. all of the above

46. Reasons why theophylline is not a “preferred” agent for long-term control include all but which of the following:
   a. has weak anti-inflammatory effects
   b. can be taken orally once or twice daily
   c. significant variability in dose and resulting level necessitating monitoring
   d. all of the above

47. Which of the statements on asthma in patients at the extremes of age is incorrect?
   a. Asthma diagnosis in infants and very young children is difficult and may require a trial of asthma medication.
   b. Goals of therapy in children include not exceeding SABA use twice daily and reducing emergency visits.
   c. Older adults are more likely to have comorbid conditions and treatments that can complicate asthma control.
   d. all of the above

48. The step-wise approach is recommended for the treatment of ____.
   a. seasonal asthma
   b. cough variant asthma
   c. both a & b
   d. neither a & b

49. Exercise-induced bronchospasm (EIB) ____.
   a. can be effectively managed by LABAs, but not with SABAs
   b. should be considered in all asthmatics
   c. frequently manifests with shortness of breath and chest pain just prior to exercise
   d. should mandate that the level or type of activity be changed in those who experience it

50. Asthma patients undergoing surgical procedures ____.
   a. have greater risk for complications during the procedure and post-operatively
   b. should be asked about latex sensitivity
   c. should receive systemic hydrocortisone at the time of heightened stress from the procedure, then tapered quickly, if they had received systemic corticosteroids during the previous 6 months
   d. all of the above

51. Pregnant women with asthma should ____.
   a. avoid asthma medications as their associated risks are greater to the fetus than poor asthma control
   b. take asthma medications to maintain disease control and avoid exacerbations
   c. rely on antibiotics and decongestants to manage symptoms rather than usual control medications
   d. have her care directed solely by her obstetrician

52. The most common cause of asthma exacerbation is:
   a. viral respiratory infection
   b. gastroesophageal reflux
   c. bacterial lung infection
   d. inhaled foreign body

53. Episodes of worsening symptoms and decreasing pulmonary function ____.
   a. require prompt treatment to correct hypoxemia, reverse airflow obstruction, and decrease recurrence
   b. should be managed according to patient specific written action plans
   c. are managed better with early recognition, which can be supported by patient monitoring and education
   d. all of the above

54. Action plans for handling asthma exacerbations ____.
   a. empowers the patient to self-manage and can facilitate early treatment (i.e. start at home, school, etc.)
   b. should be general in nature so as to accommodate many patients with various levels of control
   c. are used to instruct health professionals on patient care should they need emergency treatment
   d. are based off subjective descriptions from the patient
55. Which of the following interventions for asthma exacerbation is incorrect?
   a. initiate treatment with a LABA; may repeat once
   b. initiate treatment with inhaled SABA, repeating as necessary
   c. double ICS dose until symptoms/PEF stable for mild exacerbations
   d. systemic corticosteroids for moderate and severe exacerbations

56. Patients at risk for death from asthma include those with ___.
   a. prior intubation or admission to an ICU for asthma
   b. inability to perceive airflow obstruction
   c. 2 or > hospitalizations or 3 or > ER visits for asthma in the past year
   d. all of the above

57. The most important objective of laboratory studies for patients in the ER with suspected asthma exacerbation is to ___.
   a. evaluate for theophylline toxicity
   b. check for the presence of infection
   c. identify actual or impending respiratory failure
   d. avoid hypokalemia from SABA administration

58. Infants with asthma are more susceptible to respiratory failure due to ____.
   a. a higher incidence of viral pulmonary infections
   b. decreased pulmonary smooth muscle and peripheral airway resistance
   c. anatomical characteristics, including less elastic recoil, increased peripheral airway resistance, and insufficient collateral channels of ventilation
   d. none of the above

59. Systemic corticosteroids are indicated in patients with asthma exacerbations ___.
   a. that are moderate or severe, or require admission to the hospital
   b. incompletely respond to beta₂-agonist therapy
   c. both a and b
   d. neither a or b

60. Asthma education ____.
   a. can reduce morbidity in patients of all ages, particularly high-risk patients
   b. should be included in all steps of asthma care
   c. should include the patient’s family or caregiver and address pharmacologic regimens, environmental control strategies, detection of exacerbation, self-management, and communication with health care providers
   d. all of the above