Asthma—The National Surveillance Data and the National Asthma Education and Prevention Program’s Expert Panel Report 3

Thomas McCarter, MD, FACP

“The disease often begins in childhood and sometimes lasts until old age. It may follow an attack of whooping cough. One of the most striking peculiarities is the bizarre and extraordinary variety of circumstances, which at times induce a paroxysm. Among these local conditions, climate or atmosphere is most important.”
——William Osler, MD (1905)

Asthma was familiar to various Greek and Roman authors; however, the attacks of severe wheezing were confused with dyspnea from other causes. By the 1900s many of the key attributes of the disease state were well described, such as spasm of the bronchial muscles, swelling of the bronchial mucous membrane, and the role of inflammation. The disease was recognized to run in families, and to be influenced by provocative stimuli such as odors, flowers, hay, and emanations from animals.

Today, asthma continues to be recognized as a chronic inflammatory disease of the lungs, which typically presents with intermittent cough, wheezing, shortness of breath or dyspnea, and chest tightness, commonly occurring during the night and early morning. The underlying inflammation leads to airway hyperresponsiveness and obstruction with some degree of reversibility. This inflammatory reaction may result in sudden exacerbations and chronic progressive structural changes within the lung.

Incidence, Prevalence, and Mortality

In October 2007, the Centers for Disease Control and Prevention published National Surveillance for Asthma in the United States for the years 1980-2004. Over a 3-year period (2001-2003), an average annual 20 million persons in the United States reported having asthma. Of these, approximately 6.2 million were children (younger than age 18 years), and 13.8 million were adults. The prevalence was higher in children (8.5%) than in adults (6.7%). Rates were higher for male children (9.6%) compared with female children (7.4%); however, male adults (4.9%) had a lower prevalence than female adults (8.4%). Rates were highest in the Northeast (8.1%) compared with the Midwest (7.5%), South (6.7%), or West (6.8%). More than half of these patients reported experiencing an attack in the previous year.

For the 3-year period 2001-2003, asthma patients had an annual average of 12.3 million physician office visits, 1.3 million hospital outpatient visits, 1.8 million emergency department visits, and 504,000 hospital discharges (Figure 1).

During the same period, there were approximately 4,210 deaths annually from asthma (Figure 2). About half of these deaths occurred in persons older than 65 years of age. Approximately 200 were children younger...
than 18 years of age. Because of changes in coding practice, it is somewhat difficult to compare rates before and after 1999; however, despite linear increases in the annual asthma death rates from 1980 to 1998 and the increasing prevalence for each recent year (2001-2004), the number of asthma deaths was lower than that rate in 2000.

Despite these gains, these data show that ethnic and racial disparities in asthma outcomes persist, with greater disease impact within African American and Puerto Rican populations. Socioeconomic disparities also persist, with those below the federal poverty level reporting greater prevalence of asthma (10.3%) than those at (6.4%) or above (7.9%) this level.

In August 2007, the National Heart, Lung, and Blood Institute in cooperation with the National Asthma Education and Prevention Program (NAEPP) released Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. This panel was convened to review new information and to update reports published in 1991, 1997, and 2002. In the latest work, the panel reviewed more than 15,000 titles, 2,800 abstracts, and in excess of 2,000 full-text articles. This article attempts to summarize some of the recommendations from this 440-page report, focusing on patients 12 years of age and older, and on the diagnosis and management of asthma. Readers are encouraged to review the original document for more detailed information, including recommendations for children younger than 12 years of age, as well as excellent tools useful for improving practice.

Pathogenesis

Although there is no clear etiology of asthma, the key pathologic feature is chronic inflammation involving neutrophils, eosinophils, lymphocytes, macrophages, mast cells, and a vast number of inflammatory mediators. This inflammation leads to airway hyperresponsiveness, obstruction, and, in some cases, chronic structural changes to the airway, such as fibrosis, excess mucous production and glandular hyperplasia, hypertrophy of smooth muscle, epithelial cell injury, and new vessel formation. The acute symptoms of asthma, and sudden exacerbations, result from airflow limitation, and usually respond to bronchodilator and anti-inflammatory medications.

Airflow limitation in asthma is caused by bronchoconstriction or bronchospasm—smooth muscle contraction that narrows the airways. This may occur in response to allergic or irritant stimuli that induce immunoglobulin (Ig)E-dependent release of mediators from mast cells (histamine, tryptase, leukotriene, and prostaglandins) that directly contract airway smooth...
muscle. Similar mediator release may occur from non-IgE-mediated mechanisms, including aspirin and non-steroidal anti-inflammatory drugs, environmental stimuli (extremes of heat, cold, and humidity), exercise, and emotional stress. Bronchoconstriction in asthma is exaggerated and described as hyperresponsiveness. Anti-inflammatory treatment reduces hyperresponsiveness, thereby reducing the frequency of exacerbations and improving asthma control. With more persistent disease and prolonged inflammation, edema, excess mucous production, and structural changes may further limit airflow.

**Risk Factors**

Asthma has long been recognized to be associated with allergy and atopy. Atopy, an adverse inflammatory immune reaction involving IgE, remains the strongest identifiable risk factor for the development of asthma. Therefore, host factors such as genetic predisposition may interact with environmental stimuli generating an excessive acute and/or chronic inflammatory reaction. Distinct phenotypes of asthma have been described, such as intermittent, persistent, exercise-associated, aspirin-sensitive, and severe asthma. Viral infections also play a role as an important cause of disease exacerbations, and perhaps in the development of asthma. Some studies have shown that children with documented hospitalizations due to infection with respiratory syncytial virus have a higher incidence of asthma in later life, but others have conferred a protective effect of viral infections in early life.

Environmental risk factors such as house-dust mite, cockroach, and *Alternaria* exposures are recognized risk factors for children. Dog and cat dander have been implicated in the past; however, some studies have found early exposure to these allergens to be protective. Tobacco smoke, air pollution, occupational exposures, and diet (low intake of antioxidants and omega-3 fatty acid, as well as obesity in general) have been implicated as risk factors.

Although genetic and environmental stimuli may vary considerably, the inflammatory reaction remains consistent. The onset of asthma for most patients occurs early in life and is often associated with a parental history of the disease. In early life, asthma is more prevalent among boys; however, at puberty the ratio shifts, and the prevalence and incidence appear higher in women. Female asthmatics are also more likely to have reported attacks in the preceding year.

**Natural History**

Children in whom the onset of asthma symptoms occur within the first 3 years of life may develop deficits in lung growth associated with asthma occurrence by 6 years of age. When followed through 11 to 16 years of age, these children experience significant reduction in lung function compared with children with no history of symptoms for the first 6 years of life. Children whose symptoms begin after 3 years of age do not experience deficits in lung function. Deficits therefore seem to correlate better with the time of onset than to the duration of the disease. Deficits do not correlate to severity of symptoms or to degree of control. Not all children who wheeze will go on to develop persistent asthma. The following algorithm has been shown useful in identifying those who will:

Children in whom the onset of asthma symptoms occur within the first 3 years of life may develop deficits in lung growth associated with asthma occurrence by 6 years of age.

Children younger than 3 years of age who experienced 4 or more episodes of wheezing in the previous year will develop persistent asthma, if they have 1 of the following:

- parental history of asthma
- physician diagnosis of atopic dermatitis
- evidence of sensitization to aeroallergens or 2 of the following:
  - evidence of sensitization to foods
  - peripheral blood eosinophilia greater than or equal to 4%
  - wheezing apart from colds

**Asthma Diagnosis**

The panel defines 5 terms with regard to asthma assessment and monitoring:

- Severity is the intrinsic intensity of the disease process, measured most easily during an initial visit with a patient not receiving long-term control therapy. Severity is a useful guide to making clinical decisions regarding therapy. In patients who are already treated at the time of the initial visit, severity may be
inferred by the least amount of treatment required to maintain control.

- Control is the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met. After therapy is initiated, the degree of control achieved will determine whether adjustments in therapy are required.

- Responsiveness is the ease with which asthma control can be achieved through therapy.

- Impairment is a measure of the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced.

- Risk is the likelihood of either asthma exacerbations, progressive decline in lung function (or for children, reduced lung growth), or adverse effects from therapy.

To establish a diagnosis of asthma, the clinician should determine that episodic symptoms of airflow obstruction or airway hyperresponsiveness are present. This airflow obstruction should be at least partially reversible, and alternative diagnoses should be excluded. This determination should be made on the basis of a detailed medical history, a physical examination, and pulmonary function testing (spirometry). The medical history should identify symptoms likely caused by asthma, patterns of symptoms, family history of asthma, or a personal or family history of allergies.

Physical examination may indicate hyperexpansion of the thorax, accessory muscle use, hunched shoulders, chest deformity, wheezing, prolonged expiration, nasal discharge, congestion or polyps, atopic dermatitis, eczema, or other allergic skin conditions. Pulmonary function testing should be used to determine the presence and degree of obstruction, and the degree of reversibility. The expert panel recommends that forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and the ratio of FEV₁/FVC be measured before and after the patient inhales a short-acting bronchodilator for all patients 5 years of age or older, in whom the diagnosis of asthma is being considered.

Spirometry is preferred over measurements by a peak flow meter in physicians’ offices. The forced expiratory volume in 6 seconds (FEV₆) may be a reasonable alternative to the FVC. Airflow obstruction is indicated by a reduction in the values for both the FEV₁ and the ratio (FEV₁/FVC) relative to reference values.

### CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

**Assessing severity and initiating treatment for patients who are not currently taking long-term control medications**

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity</th>
<th>&gt;12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Intermittent</td>
<td>Persistent</td>
</tr>
<tr>
<td>≥2 days/week</td>
<td>&gt;12 years/week but not daily</td>
<td>Daily</td>
</tr>
<tr>
<td>≥2 days/week</td>
<td>≥1 year/week but not nightly</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≥24/month</td>
<td>Daily</td>
</tr>
<tr>
<td>≥2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
</tr>
<tr>
<td>≥2 days/week</td>
<td>&gt;3% per year</td>
<td>Daily</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of IEB)</td>
<td>≥2 days/week but not daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Normal FEV₁/FVC</td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>≥80% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60% predicted</td>
<td></td>
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<tr>
<td>≥40% predicted</td>
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<tr>
<td>≥20% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Normal FEV₁/FVC</td>
<td></td>
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<tr>
<td>≥80% predicted</td>
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<tr>
<td>≥60% predicted</td>
<td></td>
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<td>≥40% predicted</td>
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<tr>
<td>≥20% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/year (see note)</td>
<td>≥2/year (see note)</td>
</tr>
<tr>
<td>Relative annual risk of exacerbations may be related to FEV₁</td>
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**Recommended Step for Initiating Treatment**

(See Figure 4–5 for treatment steps.)

- Step 1:  Evaluate level of asthma control that is achieved and adjust therapy accordingly.
- Step 2:  Consider short course of oral systemic corticosteroids.

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.

- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient/caregiver’s recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.

- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**Source:** Reference 4.
or predicted values. If FVC is reduced with a normal or increased ratio (FEV₁/FVC), this pattern suggests a restrictive defect rather than an obstructive defect, making the diagnosis of asthma less likely.

Reversibility is indicated by the American Thoracic Society standards as an increase in FEV₁ of more than 200 mL and more than 12% from baseline after the inhalation of a short-acting bronchodilator. Some studies also consider an increase greater than or equal to 10% of predicted FEV₁ as an indication of reversibility. The degree of reversibility appears to correlate with the degree of airway inflammation, the risk of developing fixed airflow obstruction, and the severity or loss of lung function.

Additional studies may be appropriate based on history and physical examination findings to rule out other diagnoses (vocal cord dysfunction, cough variant asthma, allergic bronchopulmonary aspergillosis, and obstructive sleep apnea) or to identify comorbid conditions that could affect asthma control (gastroesophageal reflux disease and chronic obstructive pulmonary disease). Provocative testing with methacholine, histamine, cold air, or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal. Chest x-ray may be indicated to exclude other diagnoses.

Patients with more severe asthma may require more aggressive therapy to achieve adequate control. Severity and degree of control can usually be determined by taking a carefully directed history, physical examination, and lung function measurement. A number of standardized validated instruments have been developed to determine the severity of impairment in patients of various ages. Some patients may not accurately gauge their degree of obstruction (“poor perceivers”). They may have limited their activity to reduce symptoms or may have blamed symptoms on other factors such as age, obesity, or lack of fitness. In these patients, spirometry may more effectively quantify the degree of obstruction. Some historical factors may be valuable in assessing risk, such as emergency department visits, intensive care unit admissions, or hospitalizations in the past year. Some patients with few symptoms and little impairment may still be at risk for life-threatening exacerbations. A number of possible biomarkers are under study, but none to date have proved to be diagnostic or reliable markers of severity or risk.

Figure 3.

SAMPLE ASTHMA ACTION PLAN

Management and Self-Management

Precipitating factors such as inhalant allergens (pets, mold, seasonal pollens) exposure at home, work, or school; irritants (tobacco smoke, industrial pollutants, ozone); and viral infections should be identified, as should comorbid conditions that might aggravate asthma, such as sinusitis, rhinitis, and gastroesophageal reflux disease. Patients should be educated about how to avoid triggers, or if unavoidable, how to adjust their treatment regimen and monitoring in response to triggers.

The patient or caregiver must understand and be able to adhere to the treatment plan, including pharmacologic administration. Assessment of skills as well as education and support of self-management techniques must be integrated into all phases of clinical management.

The initial assessment of severity is made on the basis of current spirometry and the patient’s recall of symptoms over the previous 2 to 4 weeks. Severity with regard to impairment is assessed via spirometry and review of symptoms, including nighttime awakenings; need for short-acting bronchodilators for symptom relief; work or school days missed; the ability to engage in normal, desired activities; and quality-of-life assessments. Treatment decisions for children should be made on the basis of symptoms with spirometry as an additional guide. FEV₁ appears to be a useful measure indicating risk of exacerbations, whereas FEV₁/FVC appears to be a more sensitive measure of severity in the impairment domain.

The second dimension of severity is the risk of adverse events, including exacerbations and death. Patients at increased risk will require close monitoring and frequent assessment. It is important to remember that patients at any level of severity may have severe exacerbations. Predictors of increased risk include severe airflow obstruction as detected by spirometry, especially persistent obstruction; 2 or more emergency department visits or hospitalizations in the past year; history of intubation or intensive care unit admission, especially in the past 5 years; and a reported sense of danger or fear associated with asthma. Patients who are female, nonwhite, who smoke, who do not use inhaled corticosteroids (ICSs), and who are depressed or emotionally stressed are at increased risk for adverse events.

The first goal of therapy is to achieve adequate con-
control by reducing impairment. This may be accomplished by preventing symptoms (specifically daytime symptoms and nighttime awakenings), requiring infrequent use (less than or equal to 2 days per week) of inhaled short-acting bronchodilators, maintaining near-normal pulmonary function and activity levels, and meeting expectations and generating satisfaction with asthma care. The second goal of therapy is to achieve adequate control by reducing risk. This may be accomplished by preventing exacerbations and decreasing the need for emergency department visits and hospitalizations, preventing progressive loss of lung function, and providing optimal pharmacotherapy with minimal adverse effects.

Periodic assessments at no greater than 6-month intervals and ongoing monitoring are recommended to determine if goals are being met, or whether adjustments in therapy are required. Follow-up spirometry is recommended at least every 1 to 2 years after treatment has been started and symptoms have stabilized, and more frequently if necessary during periods of progressive or prolonged loss of asthma control. An FEV\(_1\) less than 60% of predicted is consistent with “severe asthma,” an FEV\(_1\) of 60% to 79% of predicted is consistent with “moderate asthma,” and 80% to 100% with “mild asthma.”

All patients should be provided a written asthma action plan based on signs and symptoms or peak expiratory flow (PEF) measurements (Figure 3). Written action plans should contain information specific to daily management and recognition of worsening asthma. Daily management action plans should include names and instructions for the use of daily medications, and actions to take to control environmental triggers. Action plans for worsening symptoms should include signs, symptoms, and peak flow measurements indicating the need for urgent medical attention; and emergency contact numbers and instructions for the physician, emergency department, and transport services.

Patient self-monitoring of PEF and symptoms are important for the effective management of asthma. Patients should be taught to recognize symptom patterns that indicate poor control and the need for more aggressive therapy. Education and support of self-management should be reinforced in all healthcare settings, including physicians’ offices, pharmacies, emergency departments, schools, community and hospital settings, and in the home. Self-management education has proved both effective and cost-effective for asthma, with increasing benefits in more severe disease. Disease management and intensive case management approaches have also been found to be cost-effective. Providers must under-
ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (≥12 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≥2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≥2/night</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta-agonist use</td>
<td>≥2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>≥80% predicted</td>
</tr>
</tbody>
</table>

**Notes:**
- Before step up in therapy:
- Regular followups
- Maintain current step.
- For side effects, consider short course of alternate treatment options.
- **Conclusion:** Requires long-term followup care
- **Risk:** Consider severity and interval since last exacerbation
- **Recommendation:** Evaluate severity and interval since last exacerbation
- **Conclusion:** Requires long-term followup care
- **Recommendation:** Evaluate severity and interval since last exacerbation

**Key:** EIB, exercise-induced bronchospasm; ICU, intensive care unit

### Medication Management

The panel categorizes asthma medications into 2 classes: long-term control medications used to achieve and maintain control of asthma, and quick-relief medications used to treat acute symptoms and exacerbations (Figure 4).

**Long-Term Control Medications (Controller Medications)**

The most effective long-term control medications are those that affect underlying inflammation, and these should be taken daily to achieve and maintain control of persistent asthma. ICSs are the most potent and effective anti-inflammatory medications currently available for the long-term control of asthma. These agents reduce the severity of symptoms, improve control, improve spirometry, diminish hyper-responsiveness, and reduce exacerbations, hospitalizations, and death, while improving quality of life. Short courses of systemic corticosteroids, given orally or intravenously, are often used to gain prompt control of the disease during exacerbations or when initiating long-term therapy; however, the lower bioavailability of ICSs confers lower risks of side effects than systemic corticosteroids. Corticosteroid effectiveness is decreased among smokers, and difficult to control asthma in some African American children may be the result of diminished corticosteroid sensitivity at the cellular level. To reduce the potential for adverse effects, ICSs may be used with a spacer device (unless breath activated), and patients may be instructed to “rinse and spit” after inhalation.
Adherence to therapy and technique in using inhalers should be assessed at every opportunity. The lowest dose that achieves control should be used. In some patients, the addition of an adjunct controller medication may allow reduction of inhaled steroid dosage. Monitoring for bone loss, supplemental vitamin D and calcium, or antiresorptive therapy may be indicated in patients with increased risk for osteoporosis. The benefits of ICS use in all age groups outweigh concerns about growth or other systemic effects (Table 1).

Cromolyn sodium and nedocromil stabilize mast cells and modulate inflammation by interfering with chloride channel functions. They are not preferred agents but may be used as alternatives in the treatment of mild persistent asthma. They may also have a role in treatment before exercise or unavoidable exposure to other triggers.

Immunomodulators, such as omalizumab, a monoclonal antibody that prevents binding of IgE to receptors on mast cells and basophils, may be used as adjunctive therapy for some patients. Clinicians who administer this agent should be prepared to treat anaphylaxis that may occur.

Several leukotriene-modifying agents are available for the treatment of asthma. Two of these are leukotriene receptor antagonists (LTRAs), montelukast and zafirlukast. A third agent, zileuton, is a 5-lipoxygenase-pathway inhibitor that requires liver function monitoring and is not approved for use in children. Although these agents are not preferred, they are effective alternative medications for mild persistent asthma or as adjunctive therapy.

Long-acting beta\textsubscript{2}-agonists (LABAs), salmeterol and formoterol, are bronchodilators that have durations of action greater than 12 hours after a single dose. They do not affect the chronic inflammation that is central to the disease process; therefore, they are not recommended for use as monotherapy. They may be used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma. LABAs are the preferred adjunctive therapy in adults and children older than age 12. They may also be used before exercise to prevent exercise-induced bronchospasm (EIB); however, chronic use is discouraged because of the risk of disguising poorly controlled persistent asthma. Use of LABAs for the treatment of acute symptoms or exacerbations is not recommended. Long-term use of LABAs in some studies has been associated with increased mortality, as reflected in the U.S. Food and Drug Administration black box warning on all of these preparations.

Methylxanthines, such as sustained-release theophylline, are mild to moderate bronchodilators and may have a mild anti-inflammatory effect. Although not preferred, theophylline may be used as an alternative therapy, and although not a preferred adjunct, it may be used in an adjunctive role with ICS. Monitoring of serum theophylline concentrations is essential.

Quick-Relief Medications (Rescue Medications)

Anticholinergic medications inhibit muscarinic cholinergic receptors and reduce intrinsic vagal tone in the airway. Ipratropium bromide provides additive benefit to short-acting beta\textsubscript{2}-agonists (SABAs) in moderate to severe asthma exacerbations, and may be used as an alternative bronchodilator in patients who do not tolerate SABAs.

SABAs such as albuterol, levalbuterol, and pirbuterol are bronchodilators that relax smooth muscle. They are the therapy of choice for relief of acute symp-
toms, exacerbations, and for the prevention of EIB. Oral systemic corticosteroids are used for moderate and severe exacerbations as an adjunct to SABAs to speed recovery and to prevent recurrence of exacerbations.

The expert panel has provided specific management recommendations and tools for 3 distinct age groups of patients. Children aged 0 to 4 years comprise one group; children aged 5 to 11 years the second group; and youths older than 12 years of age and adults comprise the third group. For each population, the EPR 3 contains recommendations and specific tools including medications approved, severity classification tools, step-therapy diagrams, as well as dosage and titration recommendation. For this document, agents for “youths greater than 12 years of age and adults” have been included for review and discussion.

Managing Exacerbations

Exacerbations are acute or subacute episodes of progressively worsening asthma symptoms characterized by measurable decreases in expiratory airflow. Milder exacerbations may be managed at home, whereas more serious exacerbations may require an unscheduled visit to the physician’s office, an emergency department visit, or a hospitalization. The most severe exacerbations may require admission to an intensive care unit for optimal monitoring with or without ventilatory support. Patients with well-controlled asthma are less prone to have exacerbations; however, they may occur even in patients with good control.

Early treatment of exacerbations is the best strategy for management. Because treatment should start immediately at recognition, patient education that includes a written action plan is essential. Patients must understand the early signs, including peak flow measurements that indicate an exacerbation, and what steps to take to withdraw from environmental triggers, to adjust therapy including initiation of a short course of oral systemic corticosteroids in some cases, and to communicate or seek urgent medical care. The expert panel no longer recommends that patients double their ICS dose when managing exacerbations. Patients who are at high risk for asthma-related death, and infants owing to their greater risk for respiratory failure, require special attention (Table 2).

The principal goals in treating asthma exacerbations should be correction of hypoxemia, reversal of airflow obstruction, and reduction of the likelihood of relapse. These 3 goals are best achieved through administration of supplemental oxygen or mechanically assisted ventilation when required, repetitive or continuous administration of SABAs, and the administration of a short course of systemic corticosteroids to patients with moderate to severe exacerbations or those who fail to promptly respond to SABAs.

Careful assessment and monitoring is necessary to achieve these goals. Monitoring may include serial measurement of lung function through spirometry or PEF, pulse oximetry, and serial assessments of signs and symptoms (several assessment tools are reviewed in EPR 3, and are available in the document).

Beginning treatment at home avoids treatment delays, prevents exacerbations from becoming severe, and adds to patients’ sense of control over their asthma. Patients should be taught to recognize symptoms of an exacerbation and to assess severity. When possible, peak flow monitoring may provide an accurate assessment of severity and response to treatment, especially in patients who are “poor perceivers” of their degree of obstruction on the basis of symptoms alone. Patients should increase their frequency of SABA use, initiate oral systemic corticosteroids, continue their dose of ICS (although doubling the dose alone is no longer recommended), and continue this more intensive regimen for several days.

The expert panel recommends that personnel involved in prehospital management and transportation begin treatment with oxygen and SABAs, without delaying transport, and that jurisdictions enable these providers to have standing orders for repeated treatments and protocols to allow consideration of anticholinergic and oral corticosteroid administration in situations involving prolonged transportation.

In the urgent care setting (emergency department or hospital), treatment should focus on oxygen to relieve hypoxemia, SABAs, and perhaps inhaled anticholinergics to relieve airflow obstruction, and systemic corticosteroids to decrease inflammation in patients who fail to immediately respond to bronchodilators alone. Patients should be evaluated and triaged immediately. Initial assessment that includes a brief history, brief physical examination, and objective measures of lung
function (FEV₁ or PEF) should be performed. Laboratory studies, electrocardiogram, and radiology studies are usually not necessary, unless comorbid conditions are present, or if diagnosis is unclear and these are needed to exclude other conditions. After treatment has been initiated with oxygen, SABAs (3 treatments spaced every 20 to 30 minutes can be given safely to most patients), ipratropium bromide, and systemic corticosteroids, a full history and physical examination may be completed.

Because of the risk of cardiotoxicity in high doses, the use of selective SABAs (albuterol, levalbuterol, and pirbuterol) is recommended. These agents may be administered via multidose inhaler with a valved holding chamber, or via nebulizer. The onset of action for SABAs is less than 5 minutes, and repetitive administration produces incremental bronchodilation. Most patients will have a significant response after the first dose, and 60% to 70% will respond sufficiently to 3 doses to allow discharge. The addition of ipratropium bromide (by metered dose inhaler or nebulizer) to SABAs results in additional bronchodilation in the emergency setting; however, ongoing treatment for patients who require hospitalization is not recommended.

Patients with moderate to severe exacerbations who do not respond to initial therapy should be started on a short course of systemic corticosteroids, to speed the resolution of airway obstruction, and to reduce the rate of recurrence. The less invasive use of oral preparations is as effective as intravenous formulations and is therefore preferred. A 5- to 10-day course may prevent early relapse. The expert panel does not recommend methylxanthines,
antibiotics (except as needed for comorbid infections), aggressive hydration, chest physical therapy, mucolytics, or sedation. Serial evaluations of symptoms and lung function are necessary to ensure that patients are responding to therapy and to determine final disposition (see sidebar: Managing Exacerbations of Asthma, p 45).

For patients being discharged from the hospital inpatient setting, medications should be adjusted to the outpatient regimen, and the patient should be monitored for 24 hours to ensure stability.

The response to therapy is a better predictor of the need for hospitalization than is the severity of the exacerbation on presentation. Repeat assessments should be performed after the initial dose of a SABA, and after 3 doses. The patient’s subjective response to therapy, physical findings, FEV$_1$ or PEF, pulse oximetry, and perhaps arterial blood gas should be assessed. The decision for further hospitalization is based on the duration and severity of symptoms, the severity of airflow obstruction, the response to treatment, severity and course of previous exacerbations, medication use at time of exacerbation, access to care and medications, the presence of comorbid conditions that could complicate recovery, and support available to the patient at home.

EPR 3 recommends cut points established in 1991 for FEV$_1$ or PEF to determine discharge plans from the emergency setting. The goal for discharge from an emergency setting is an FEV$_1$ or PEF greater than or equal to 70% of predicted or personal best. FEV$_1$ or PEF of 40% to 69% indicates an incomplete response to therapy and possibly a need for continued treatment in a monitored setting. An FEV$_1$ or PEF of less than 40% of predicted indicates a severity level where adjunct therapies may be indicated. These cut points differ from those used to determine long-term control. The panel recognizes the limited value of these measures in young children and in the most severe exacerbations.

In severe situations, intravenous magnesium sulfate and heliox may play a role in preventing intubation. Other interventions that may be considered but are supported by less evidence include LTRAs and noninvasive ventilation. The expert panel does not recommend the use of intravenous isoproterenol because of the risk of myocardial toxicity. Even without intubation, patients who have severe exacerbations and are slow to respond to therapy may benefit from admission to an intensive care unit, where they can be monitored closely and intubated if necessary.

The need for intubation is a determination based on clinical judgment. Intubation should not be delayed after it has been deemed necessary. Because intubation is difficult in asthma patients, semielective intubation performed by a physician with extensive experience in airway management is recommended before respiratory arrest occurs. Worsening airflow obstruction, worsening ventilation or respiratory muscle fatigue, evidenced by the inability to speak, altered mental status, intercostal retraction, or a P$_{CO_2}$ of greater than or equal to 42, may signify impending respiratory failure. The recommended ventilator strategy is that of “permissive hypercapnea” or “controlled hypoventilation,” which provides adequate oxygenation and ventilation while minimizing barotrauma owing to high airway pressures. This strategy may require high F$_{O_2}$ settings, and treatment of respiratory acidosis with intravenous sodium bicarbonate. Consultation or comanagement by physicians with extensive experience in ventilator management may be indicated.

When patients stabilize sufficiently to be discharged from the emergency or hospital setting, medications and education on their use (including inhaler technique), follow-up appointments, a peak flow meter (and instruction on its use), and an emergency discharge plan for recognizing and managing relapse should be provided. Patients who have a rapid response to initial therapy should be observed for 30 to 60 minutes to ensure stability of response before discharge. Discharge is usually appropriate if FEV$_1$ or PEF has returned to greater than or equal to 70% of predicted or personal best, and if symptoms are minimal or absent. Patients who have an incomplete response (FEV$_1$ or PEF 50%-69% of predicted or personal best) and mild symptoms should be individually assessed for discharge readiness.

Patients should be prescribed sufficient medications to continue treatment after discharge. Those who receive corticosteroids should continue therapy for 3 to 10 days. For courses less than 10 days, and for patients taking concurrent ICSs, there is no need to taper the dose. ICSs in addition to oral therapy have been shown to reduce risk or relapse. The expert panel recommends that ICS therapy should be initiated at discharge even in patients concurrently receiving a short course of systemic steroids. Follow-up care with the patient’s primary care physician or an asthma specialist within 1 to 4
weeks should be emphasized and facilitated. Emergency providers should communicate with the patient’s regular provider, and encourage patients to contact their provider during the first 3 to 5 days after discharge.

For patients being discharged from the hospital inpatient setting, medications should be adjusted to the outpatient regimen, and the patient should be monitored for 24 hours to ensure stability. Discharge medications, education regarding their use, follow-up appointments, written plan, and a peak flow meter with instructions on its use should be provided as described above for discharges from the emergency setting.

**Special Considerations in Management**

The expert panel identifies and provides specific recommendations for 3 topics identified as “Special Situations.” These include Exercise-Induced Bronchospasm, Asthma in Pregnancy, and Surgery in the Asthma Patient.

**Exercise-Induced Bronchospasm**

Exercise may be the only precipitant of asthma symptoms in some patients, yet EIB should be anticipated in all asthma patients. EIB is a bronchospastic event that is caused by loss of heat, water, or both from the lung owing to hyperventilation of cool, dry air during exercise. Some studies suggest that inflammatory mediators are involved in the response. EIB usually occurs during or minutes after activity, with symptoms reaching a peak 5 to 10 minutes after stopping the activity, and resolving in another 20 to 30 minutes. Some studies have documented a refractory period of less than 1 hour after EIB, allowing for an asthma-symptom–free interval after warm-up exercises. It is unclear whether a late-phase reaction occurs hours after exercise.

A history of asthma symptoms or endurance problems during exercise suggests EIB. An exercise challenge resulting in a 15% decrease in PEF or FEV₁ (with measurements taken before and after exercise at 5-minute intervals) is compatible with EIB. Adequate control should enable the patient to participate in any chosen activity, without experiencing symptoms; therefore, EIB should not limit either participation or success in vigorous activities.

Evidence suggests that treatment with anti-inflammatory medications will reduce airway hyperresponsiveness, and the frequency and severity of EIB. Patients should be monitored regularly to ensure that they have no other symptoms of asthma, or reductions in PEF or spirometry in the absence of exercise, because EIB may be an indication of poorly controlled asthma in need of treatment adjustments.

Pretreatment before exercise with various rescue or controller medications may be effective. SABAs will prevent EIB in more than 80% of patients, and may be helpful for 2 to 3 hours. LABAs can be protective for up to 12 hours; however, daily use is associated with a shortening of the duration of protection, even when used in conjunction with ICSs. Frequent and chronic use of LABAs may disguise poorly controlled persistent asthma, which should be controlled with daily anti-inflammatory medication, and therefore, should be discouraged.

**Surgery and Asthma**

Asthma patients may be at an increased risk for some complications during or after surgical procedures. Bronchospasm may be triggered by intubation with subsequent hypoxemia or hypercarbia. Impaired effectiveness of cough may predispose patients to atelectasis and pulmonary infections. Latex and medication sensitivities may be more pronounced in this population.

The expert panel recommends that asthma patients should be evaluated prior to surgery with special attention to their recent symptoms, medication use, and measurement of pulmonary function. Attempts should be made to improve lung function preoperatively, with
a goal toward normalizing FEV₁ or PEF to either their predicted values or their personal best level. A short course of oral systemic corticosteroids may be necessary to optimize pulmonary function.

Patients who have received oral corticosteroids for longer than 2 weeks in the past 6 months, and some patients on a long-term high dose of corticosteroids may require 100 mg hydrocortisone intravenously (stress dose steroids) every 8 hours during the surgical period to mediate the effects of adrenal suppression. In stable postoperative patients, the dose may be reduced rapidly within 24 hours after surgery.

The working group encourages monitoring of asthma on a monthly basis during prenatal visits, through symptom reporting and spirometry or peak flows.

Pregnancy and Asthma
In 2005, the NAEPP “Working Group Report on Managing Asthma During Pregnancy” released recommendations regarding pharmacologic treatment. This report and the expert panel emphasize that maintaining adequate control of asthma during pregnancy is important for the health and well-being of both the mother and her baby. Maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight infants. More severe asthma correlates with higher risk, whereas better-controlled asthma correlates with lower risk. It is safer for pregnant women and their infants to be treated with asthma medications than to experience symptoms and exacerbations.

Because asthma control may improve, worsen, or remain unchanged over the course of pregnancy, ongoing monitoring and adjustments to the treatment regimen may be required to maintain pulmonary function, blood oxygenation, and oxygen delivery to the developing fetus. The working group encourages monitoring of asthma on a monthly basis during prenatal visits, through symptom reporting and spirometry or peak flows.

Albuterol is the preferred SABA because it has an excellent safety profile and it has the most available data related to safety during human pregnancy. ICSs are the preferred long-term control medication. Among ICSs, budesonide is preferred because it has the most available safety data in pregnancy, and because the available data are reassuring; however, no data suggest that other ICS preparations are unsafe during pregnancy. Cromolyn has an excellent safety profile, but it has limited effectiveness compared with ICSs. Data on the safety and effectiveness of LTRAs and LABAs in pregnancy are limited. For treatment of associated allergy symptoms, intranasal corticosteroids are recommended and have a low risk of systemic effect, and the current second-generation antihistamines of choice are loratadine and cetirizine.

Public Health Issues

Although influenza vaccination does not improve asthma control or symptoms during an exacerbation, the expert panel recognizes that asthmatic patients have a higher risk of adverse outcome from a severe illness with influenza. Therefore it is recommended that all asthma patients undergo annual influenza vaccination.

Home-based allergen-reduction interventions focused on reducing allergens through HEPA-filter vacuum cleaners, washing linens in hot water, mattress covers, and pest control have been associated with improved control. Computer-based education and self-management training programs have also been shown in several studies to improve control. Campaigns to reduce exposure to tobacco smoke, especially for pregnant women and parents, have been shown to affect childhood control and severity, especially in children younger than age 3, in whom severity may compromise lung growth. These results also support public health campaigns to reduce environmental tobacco smoke exposure in all public areas.

EPR 3 discusses some of the racial and ethnic disparities as well as the cultural challenges that must be overcome to further improve outcomes. The panel recommends heightened awareness of cultural barriers, as well as modification of educational and communication strategies to eliminate these barriers. Some studies have shown that African American and Hispanic children with more severe asthma than white children used less anti-inflammatory medication. Other studies have shown disparities in patterns of follow-up care after emergency visits. Thus underuse or reduced access to preventive therapy may contribute to some of the outcome disparities. Financial barriers may play a role, as may disparities in health literacy, and provider practice policies (bilingual providers, diversity training, continuity of care, and comanagement practices). A large pro-
portion of ethnic and racial minorities live in urban areas, where exposure to indoor allergens can be high, and where effective mitigation strategies could significantly reduce symptoms. The degree of interaction between race, ethnicity, and socioeconomic status on asthma morbidity and mortality remains a controversial and active area of exploration. Biologic and pathophysiologic differences between ethnic groups are also more commonly recognized, independent of socioeconomic and educational influences.

**Stakeholder Issues**

The National Surveillance for Asthma and EPR 3 are very important documents to all stakeholders in the healthcare system. They provide guidance with regard to screening, diagnosis, and management of a disease that is both common and increasing in prevalence. With better understanding of pathophysiology and better methods for achieving control, mortality seems to be improving. Patients and providers must work to develop a partnership for comanagement that is based on strong evidence of effectiveness. Payors must ensure that financial barriers to appropriate screening, diagnosis, and monitoring tools, as well as controller and rescue therapies are nonexistent. Regulators and public health authorities must ensure support and funding of school-based and community-based best practices to continue to erode mortality and morbidity, especially in high-risk populations. We must all continue to correct environmental risk factors that affect this and other populations. The authors encourage all readers to review these documents from the perspective of the role they can play with regard to this condition.

**AHDB Stakeholder Perspective**

Asthma remains a serious health concern today. Affecting people of all ages around the world, uncontrolled asthma leads to a poor quality of life, and may also be fatal. In this issue of AHDB, a focus article reviews highlights of the recommendations made by the Expert Panel of the National Asthma Education and Prevention Program (NAEPP). The author, Dr. McCarter, successfully distills the key points from the comprehensive document and provides information that will help asthma patients to better control their disease.

The Expert Panel Report 3 (EPR 3) builds on the key points from its previous reports. In 1991, EPR 1 focused on the treatment of asthma as an inflammatory condition of the lung. EPR 2 came 6 years later and emphasized the importance of early diagnosis of asthma in hopes of preventing loss of lung function over time. Since the last update from 2002, EPR 3 has taken the vast amount of information that has accumulated in the asthma literature to produce a

**References**


For inquiries or comments, please e-mail editorial@AHDBonline.com.
scientific document detailing key changes in medical therapy and introducing novel approaches to asthma care management. The new guidelines stress the importance of the longitudinal assessment of asthma, as frequent, close monitoring via spirometry may help reduce the risk of exacerbation.

The anticipated outcome from the dissemination of this report is that healthcare providers will be able to manage their asthma patients more effectively, reducing both the economic and social burden of this disease. Indeed, one can project that the many stakeholders intimate to the asthma care delivery system will benefit to some degree. First and foremost, patients with asthma will be assured that the new guidelines incorporate medication safety as well as efficacy in its treatment recommendations. Healthcare providers will be satisfied that the management strategies of the EPR 3 represent evidence-based, consensus-driven decisions derived from current literature. Purchasers of healthcare will gain knowledge that there exists a standard of care in the treatment of asthma and may use the information to critically assess the performances of different health plans in their respective approaches to asthma management. However this important document will be utilized, it stands clear that its content will help guide the clinical care of asthmatic persons towards the best possible outcome.

Joseph G. Dizon, MD
Chief, Department of Allergy and Immunology
Kaiser Permanente-West Los Angeles

References