MTM essentials for asthma management: Part 1

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Abstract

Inflammation is central in the pathophysiology of asthma and is a multicellular process. Bronchoconstriction is the dominant physiological event leading to the clinical symptoms of asthma, which most commonly include wheezing, cough, and dyspnea. As asthma progresses over time, the disease becomes more persistent, and inflammation becomes more destructive. The development of asthma is multifactorial; it depends on the interaction of genetic predisposition and environmental factors, and no independent factor alone accounts for the disease. Assessment of asthma severity and control is based on both impairment and risk and helps to guide proper pharmacologic treatment according to the stepwise approach. Nonpharmacologic interventions are also important in asthma management, namely avoidance of environmental triggers and the treatment of comorbidities associated with asthma symptoms.

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Faculty Disclosure: Drs. Linder and Sobieraj have no actual or potential conflict of interest associated with this article.

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EDUCATIONAL OBJECTIVES

Goal: The goal of this activity is to introduce the pharmacist to the pathophysiology and clinical presentation of asthma and to review the assessment of asthma severity and control so that these factors can be applied to patient care activities.

After participating in this activity, pharmacist should be able to:

- Discuss the pathophysiology of asthma and describe differences between pediatric- and adult-onset asthma
- Describe the clinical presentations of asthma
- Describe assessment methods to determine the control and severity of asthma symptoms in adult and pediatric patients
- Discuss nonpharmacologic options for the management of asthma in adult and pediatric patients

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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CPE SERIES: MTM FOR THE PATIENT WITH RESPIRATORY DISEASE

Welcome to the CPE series, Medication Therapy Management for the Patient with Respiratory Disease, which was designed for pharmacists who take care of patients with respiratory disease. Beginning in April 2015 and continuing through December 2015, pharmacists can earn up to 18 hours of CPE credit with 9 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and Drug Topics.

This series kicks off this month with MTM essentials for asthma management, covering the pathophysiology of asthma, clinical presentations of asthma, assessment methods, and nonpharmacologic management options. In May the second part of MTM essentials for asthma management includes the step-care approach of management, pharmacologic options for adults and children, adherence issues, and ways to minimize health disparities in asthma care.

In June and July, the focus shifts to MTM essentials for chronic obstructive pulmonary disease (COPD) management. The August CE activity is a primer on inhalers and nebulizers. In September, pharmacists have the opportunity to learn about allergic rhinitis management. In October, the CE activity covers MTM essentials for cold, flu, and sinusitis management. The November CE activity includes drug-induced pulmonary disease recognition and management and idiopathic pulmonary fibrosis. The series concludes in December with a focus on MTM essentials for cough management.

The series also offers application-based and practice-based activities in 2016.

Introduction

Millions of Americans suffer from asthma, a chronic airway disease with obstruction that is reversible. In the United States, an estimated one in 12 adults (8%) and one in 10 children (10%) had asthma in 2009, which represents an increase of more than four million patients diagnosed since 2001. Children aged five years to 17 years have the highest prevalence of asthma across all age groups. Females are more likely than males to have asthma, and among ethnic groups, asthma is most prevalent in non-Hispanic blacks. Tremendous healthcare costs are associated with asthma: each patient with asthma cost the United States approximately $3,300 per year, totaling $56 billion in 2007.

Currently, asthma management is based on the 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma. These guidelines are coordinated by the National Heart, Lung, and Blood Institute and provide a framework for the management of asthma across all ages. There are four over-arching components of asthma management used to organize these guidelines: measures of assessment and monitoring, education for a partnership in asthma care, control of environmental factors and comorbidities, and pharmacologic therapy. Pharmacists are well trained and positioned to be involved in all four components of care which will be reviewed over the next several issues. The NAEPP EPR-3 will be the basis of the material presented in this article and in the next part of this series, to be published in May.

Pathophysiology

Inflammation, which is central in the pathophysiology of asthma, is a multicellular process involving mainly lymphocytes, mast cells, eosinophils, neutrophils, dendritic cells, and a variety of proinflammatory mediators. The interaction of these cell types with the airways eventually results in the characteristic features of the disease: bronchial inflammation and airflow limitation. The processes by which these interactions lead to the clinical manifestations of asthma are not entirely understood. However, inflammation remains a consistent component despite the distinct phenotypic patterns of asthma, and the cellular profile and response of the inflammatory cells in asthma also remain consistent.

Lymphocytes play an important role in the initiation of the inflammatory response through the release of specific cytokines, which results in the recruitment and survival of eosinophils and in the maintenance of mast cells in the airways. Current evidence suggests that a shift toward the Th-2 cytokine profile (eg, interleukin-4 [IL-4], IL-5, and IL-13) is associated with the eosinophilic inflammation that is characteristic of asthma and may help to explain the presence of eosinophils, the production of immunoglobulin (IgE), and the development of airway hyperresponsiveness in patients with this condition. Additionally, there is some evidence that asthmatic inflammation is characterized by a predominance of Th-2 lymphocytes over Th-1 cells.

In addition to lymphocytes, other cell types play a role in the inflammatory response. Mast cells may be linked to airway hyperresponsiveness in airway smooth muscle and may release a large number of cytokines to promote inflammation. Eosinophils usually exist in abundance in the airways of most patients with asthma; increased eosinophil concentration is often correlated with greater asthma severity. Eosinophils contain inflammatory enzymes, produce leukotrienes, and express proinflammatory cytokines. Dendritic cells function as antigen-presenting cells that interact with allergens from the surface of the airways and ultimately stimulate the creation of Th-2 cell production. Studies have shown that neutrophils are increased in the airways and sputum of patients with severe asthma, particularly during acute asthma attacks. However, the role of neutrophils in the development of asthma remains unclear.

Bronchoconstriction is the dominant physiological event leading to the clinical symptoms of asthma. Acute exacerbation of asthma is characterized by rapid bronchial smooth muscle contraction and subsequent narrowing of the airway to decrease exposure to irritants or allergens. This response is mediated by an IgE-dependent release of a variety of proinflammatory...
occur, leading to airway remodeling and permanent structural changes can further limit airflow in affected patients.2 Permanent structural changes can include edema, mucus hypersecretion, formation of mucus plugs, and hyperplasia of smooth muscle ultimately to progressive loss of function.2,7

mediators from mast cells that directly contract smooth muscle in the airway. Environmental stimuli such as exercise, cold air, stress, and irritants can also lead to acute airway obstruction.2 Although likely related to airway inflammation, the mechanisms by which such environmental stimuli lead to bronchoconstriction are not well defined. Exaggerated bronchoconstriction in response to various stimuli, characterized as airway hyperresponsiveness, can also occur.2

As asthma progresses over time, the disease becomes more persistent and inflammation becomes more destructive. Pathophysiologic changes including airway edema, mucus hypersecretion, formation of mucus plugs, and hyperplasia of smooth muscle further limit airflow in affected patients.2 Permanent structural changes can occur, leading to airway remodeling and

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### TABLE 1

#### CLASSIFYING ASTHMA SEVERITY IN CHILDREN AGED 11 YEARS AND YOUNGER

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ages 0-4</td>
<td>Ages 5-11</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>0</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>N/A</td>
<td>Normal FEV1 between exacerbations &gt;80%</td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids (consider severity and interval since last exacerbation)</td>
<td>0-1/year (see notes)</td>
<td>≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting &gt;1 day AND risk factors for persistent asthma</td>
</tr>
</tbody>
</table>

**Abbreviations:** FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient’s/caregiver’s recall of previous 2-4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient’s asthma is better or worse since the last visit. 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.

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response and create a Th-1/Th-2 equilibrium. According to this theory, a child with an overexpression of Th-2 may be predisposed to the production of IgE antibodies to key environmental antigens. This complex interaction, termed a gene-by-environment interaction, occurs when the susceptible host is exposed to environmental factors that are capable of generating IgE.

Environmental exposure and lifestyle may also lead to a predisposition to the development of asthma. Respiratory infections and airborne allergens are two major factors that influence the development and persistence of asthma. Infection with respiratory syncytial virus (RSV) and parainfluenza virus during infancy has been associated with the development of asthma. Long-term prospective studies of children with documented RSV infection have demonstrated a 40% incidence of persistent respiratory symptoms consistent with asthma. Conversely, there is also evidence to support the theory that early infection with measles virus, RSV, or repeated viral infection can elicit a protective effect against the development of asthma. Exposure to environmental allergens such as dust mites and animal dander has also been analyzed in several studies. Although it may seem likely that the intensity of exposure to dust mites and dander may affect a person’s risk for the development of IgE antibodies, more recent evidence suggests that exposure to such allergens early in life may actually protect against the development of asthma. Conversely, other studies evaluating exposure to dust mites and cockroaches have described an association between sensitization and the development of asthma. Exposures to such allergens have the potential to promote persistent airway inflammation and therefore increase the likelihood of exacerbation; as such, it is generally recommended that patients avoid such potential triggers, as discussed below.

Additional factors that have been associated with the development of asthma include tobacco smoke, air pollution, and obesity. Tobacco smoke has consistently been shown to influence the incidence of asthma. Air pollutants such as ozone and particulate matter have been linked to asthma exacerbations and increased hospitalizations; however, whether air pollution also contributes to the initial development of asthma remains unclear. Studies to date investigating the effect of inhaled pollutants on children living within 100 to 400 meters of highways or 50 to 90 meters of major roads have shown that these children are at an increased risk for wheezing but not for airway hyperresponsiveness. Finally, rates of obesity and asthma have increased in a parallel manner; however, the interrelationship between obesity and asthma remains uncertain.

**Clinical Presentation and Diagnosis**

The most common triad of asthma symptoms includes wheezing, cough, and dyspnea, although not all of these symptoms must be present to warrant a diagnosis. Nonpulmonary manifestations of asthma are also noteworthy. Signs of atopy or allergic rhinitis, such as conjunctival congestion and inflammation, ocular shiners, a transverse crease on the nose associated with allergic rhinitis caused by constant rubbing, and pale violaceous nasal mucosa may be present in patients with asthma. Skin manifestations may include atopic dermatitis, eczema, and other signs of allergic skin conditions.

Wheezing is the most common symptom associated with asthma. This wheezing, which occurs as a musical, high-pitched, whistling sound produced by prolonged airflow turbulence, results from smooth muscle contraction, mucus hypersecretion, and mucous retention. In patients with mild asthma, wheezing usually occurs only at the end of expiration. In cases of more severe asthma, wheezing occurs throughout the entire expiration. During a severe asthmatic episode, wheezing can occur during both inspiration and expiration; however, the intensity of wheezing does not correlate well with the severity of airway narrowing. During the most severe episodes, wheezing may be entirely absent because of the critical limitation of airflow that is associated with both respiratory muscle fatigue and airway narrowing. Although wheezing is one of the most common symptoms of asthma, it is not necessary for the diagnosis of asthma. Patients with asthma may present with obstruction primarily in the smaller airways, without notable wheezing.

In some patients, cough may be the only apparent symptom of asthma, especially in cases of nocturnal asthma or exercise-induced bronchospasm (EIB). This cough results from the combination of airway narrowing, mucus hypersecretion, and the hyperresponsiveness seen with airway inflammation. Cough can also appear as a consequence of nonspecific inflammation after superimposed viral infections in asthmatic patients. Because of airway narrowing and increased velocity of airflow in the airways, cough provides a means to clear collected mucus and particles from the narrowed airways. The cough is usually nonproductive and nonparoxysmal and often occurs nocturnally.

Dyspnea and chest tightness occur as a result of greater muscular effort required to overcome increased airway resistance. Hyperinflation from airway obstruction re-
Inflammation that may indicate nighttime symptoms is associated with an increase in bronchoconstriction between 4 AM and 6 AM and that the presence of symptoms just once or twice a month, whereas patients may experience nighttime symptoms associated with asthma. If the patient may feel breathless while speaking. Additionally, studies have shown that bronchoconstriction is highest between 4 AM and 6 AM and that the presence of nighttime symptoms is associated with an increase in inflammation that may indicate uncontrolled disease.

Some patients may present exclusively with EIB; in others, EIB is present along with asthma symptoms outside of exercise. Although the term implies that exercise is the cause of asthma symptoms, physical exertion that may not traditionally be considered “exercise,” such as walking up a flight of stairs, may precipitate asthma symptoms. Patients with EIB typically present with the three main symptoms characteristic of asthma: wheezing, cough, and dyspnea. These symptoms may also be accompanied by sore throat and gastrointestinal upset. Initially during exercise, bronchodilation occurs. For individuals with EIB, after approximately 10 minutes of exercise, bronchoconstriction supersedes, leading to the classic symptoms associated with asthma. If the exercise period is shorter, symptoms may develop up to 5 to 10 minutes after exercising. The occurrence of such symptoms may be attributed to the intensity of exercise, seasonal changes, and the ambient temperature and humidity in the environment in which an individual exercises.

Aside from the day-to-day clinical presentation of a patient, acute worsening of symptoms can occur and are considered an exacerbation of asthma. During an acute asthma exacerbation, patients experience increasing chest tightness, wheezing, and dyspnea that are uncontrolled or poorly relieved by a rescue inhaler. In a mild exacerbation, patients may feel out of breath after physical activity. They can usually talk in full sentences and are able to lie down in a flat position. In moderately severe episodes, the respiratory rate is increased, requiring the use of accessory respiratory muscles. On examination, loud expiratory wheezing can be heard and the patient may feel breathless while speaking. Additionally, pulsa paradoxus, a decrease in arterial systolic pressure of 10 mmHg or more during inspiration, may be present.

In severe exacerbations, patients may be so breathless that they are unable to speak in complete sentences, and they may become cyanotic. Patients often present with tachypnea, tachycardia, and pulsa paradoxus accompanied by markedly decreased spirometric values, decreased peak expiratory flow and arterial blood gases suggesting hypoxemia, and low partial pressure of carbon dioxide (pCO₂) due to hyperventilation. As the episode becomes more severe, profound diaphoresis, confusion, and agitation may occur concomitantly with an increase in pCO₂; this is an indication of impending respiratory failure, requiring immediate monitoring and therapy.
The presentation of asthma in the pediatric population may be vaguely atypical from the presentation in the adult population. Pediatric patients with asthma tend to have more nocturnal symptoms and often cough after midnight and during the early hours of the morning. Symptomatic presentations can vary in other nonspecific forms, such as recurrent bronchitis, bronchiolitis, pneumonia, and croup. In some children, asthma presents as a persistent cough with colds. Asthma is common in children with recurrent bronchitis and is the most common underlying diagnosis in children with recurrent pneumonia. In addition to typical findings during acute asthma attacks, pediatric patients may display additional signs and symptoms. During a moderately severe asthmatic episode, infants will exhibit feeding difficulties and have a shorter, softer cry. In severe episodes with imminent respiratory arrest, children will appear to be significantly drowsy and confused.

The diagnosis of asthma is based on the presence of symptoms suggestive of asthma and confirmation of reversibility of airway obstruction through spirometry. A detailed medical history and physical examination are used to establish a clinical presentation consistent with asthma. However, since many asthma symptoms are nonspecific and subjective in nature and some patients have a poor perception of their airflow obstruction, spirometry is used to objectively diagnose asthma. Spirometry is indicated in patients who have symptoms suggestive of asthma and confirms reversibility of airway obstruction. Lastly, the clinician should exclude differential diagnoses, some of which include allergic rhinitis and sinusitis, viral bronchiolitis, heart disease, recurrent cough of a differing etiology, and aspiration.

Assessment of asthma severity
Despite the variety seen among cases of asthma, the process by which the severity of this condition is assessed remains the same. The severity of asthma is defined by the intrinsic intensity of the disease process and can be classified as either intermittent or persistent. Within the category of persistent asthma, there are three subcategories: mild, moderate, and severe. Once a diagnosis of asthma is made and ideally before a patient is prescribed long-term controller medications, the severity of asthma should be determined to properly guide the initial selection of pharmacotherapy based on the stepwise approach. If a patient is already taking long-term controller medications, the severity of asthma can be inferred by the lowest intensity of medication needed to maintain asthma control. In general, the initial drug regimen’s intensity in terms of dose, frequency, and number of medications increases as asthma severity increases. Of note, the NAEP EPR-3 guidelines divide the assessment of severity and control and the stepwise approach to pharmacotherapy by age, with three distinct sets of recommendations: recommendations for patients aged four years and younger, for patients aged five to 11 years, and for pa-

### TABLE 3

**ASSESSING ASTHMA CONTROL IN CHILDREN AGED 11 YEARS AND YOUNGER**

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ages 0-4</td>
<td>Ages 5-11</td>
<td>Ages 0-4</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week but not more than once on each day</td>
<td>&gt;2 days/week or multiple times on ≤2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤3/night</td>
<td>&gt;4/night</td>
<td>&gt;5/night</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Lung Function</td>
<td>N/A</td>
<td>&gt;80%</td>
<td>N/A</td>
</tr>
<tr>
<td>• FEV1 (predicted) or peak flow personal best</td>
<td>N/A</td>
<td>&gt;80%</td>
<td>N/A</td>
</tr>
<tr>
<td>• FEV1/FVC</td>
<td>N/A</td>
<td>&gt;80%</td>
<td>N/A</td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1x/year</td>
<td>2-3x/year</td>
<td>≥2x/year</td>
</tr>
<tr>
<td>Reduction in lung growth</td>
<td>N/A</td>
<td>Requires long-term followup</td>
<td>N/A</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table Notes:
- **Well Controlled**: Symptoms controlled with minimal interference and no exacerbations require oral systemic corticosteroids.
- **Not Well Controlled**: Symptoms are present daily or multiple times per day requiring oral systemic corticosteroids.
- **Very Poorly Controlled**: Symptoms are present throughout the day, requiring systemic corticosteroids and frequent exacerbations.

### Pause & Ponder

**What are some suggestions that can be made to a patient with asthma and sensitivities to outdoor allergens in order to decrease exposure?**
Impairment

- **Symptoms**: ≤2 days/week (well-controlled), >2 days/week (poorly controlled), throughout the day (very poorly controlled).
- **Nighttime awakenings**: ≤2x/month (well-controlled), 1-3x/week (poorly controlled), ≥4x/week (very poorly controlled).
- **Interference with normal activity**: None (well-controlled), some limitation (poorly controlled), extremely limited (very poorly controlled).
- **Short-acting beta-agonist use for symptom control (not prevention of EIB)**: ≤2 days/week (well-controlled), >2 days/week (poorly controlled), several times per day (very poorly controlled).
- **FEV1 or peak flow**: >80% predicted/personal best (well-controlled), 60-80% predicted/personal best (poorly controlled), <60% predicted/personal best (very poorly controlled).

Risk

- **Exacerbations requiring oral systemic corticosteroids**: 0-1/year (well-controlled), ≥2/year (poorly controlled). (Note: ≥2/year in the past year may be considered the same as patients who have not well-controlled asthma, even in the absence of impairment levels consistent with not well-controlled asthma.)
- **Progressive loss of lung function**: Evaluation requires long-term followup care.
- **Treatment-related adverse effects**: Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient’s report of previous 2–4 weeks and by spirometry or peak-flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient’s asthma is better or worse since the last visit.
- At present, there are inadequate data to compare frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who have ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not well-controlled asthma, even in the absence of impairment levels consistent with not well-controlled asthma.

**Abbreviations:** ATAQ, Asthma Therapy Assessment Questionnaire; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; EIB, exercise-induced bronchoconstriction; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; N/A, not applicable.

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

**Notes:**
- Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
- If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

**Source:** Reprinted with permission from the National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services (Ref 2).

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**TABLE 4**

**ASSESSING ASTHMA CONTROL IN PATIENTS AGED 12 YEARS AND OLDER**

<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><strong>Impairment</strong></td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>FEV1 or peak flow</td>
<td>&gt;80% predicted/personal best</td>
</tr>
<tr>
<td><strong>Validated questionnaires</strong></td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75*</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>0-1/year</td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term followup care.</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
</tr>
</tbody>
</table>
The recommendations suggest that a patient’s asthma severity should be classified in the most progressive category based on the overall severity assessment across both domains of impairment and risk. For example, if a 15-year-old patient reports impairment symptoms consistent with moderate persistent asthma but the risk is consistent with intermittent asthma, the final severity assessment would categorize this case as moderate persistent. Based on the most severe classification of asthma, the guidelines also recommend which corresponding drug regimens should be initiated using a stepwise approach, again dividing these recommendations into the three age categories previously mentioned. In general, patients with intermittent asthma are started on step 1 therapy; those with mild persistent asthma are started on step 2 therapy; those with moderate persistent asthma are started on step 3 therapy; and those with severe persistent asthma are started on step 3, 4, or 5 therapy depending on the patient’s age. Further discussion of the stepwise approach to asthma treatment will be presented in the May issue of this series.

Severity assessment can be particularly challenging in the lowest age category of four years and younger, and the diagnosis of asthma at this age is often not definitive. A trial of pharmacotherapy is often used with close monitoring to determine whether symptoms improve and are therefore likely to be asthma related. Risk is often more closely associated with morbidity as children are often symptom free between exacerbations. Patients aged four years or younger are considered to have persistent asthma based on the risk domain if they have experienced two or more exacerbations requiring corticosteroids in the previous six months; if they have consistently required symptomatic treatment for more than two days per week for four weeks or longer; or if they have experienced four or more episodes of wheezing lasting more than one day over the previous year plus a parental history of asthma, diagnosed atopic dermatitis, sensitivity to aeroallergens, or at least two of the following: food sensitivities, eosinophilia, or wheezing aside from colds. For the other two age categories, asthma severity based on risk is considered to be persistent when the patient has had two or more exacerbations requiring systemic corticosteroids during the previous year.

### Assessment of asthma control

Once a patient is properly assessed for asthma severity and pharmacotherapy has been initiated using the stepwise approach, the clinician’s focus should shift from the assessment of asthma severity to the assessment of asthma control. Asthma control is described as the degree to which an individual patient’s asthma goals have been met and symptoms minimized by pharmacotherapy. Similar to the assessment of asthma severity, the assessment of control is specific to the age of the patient and uses the same three age categories discussed previously [Tables 3 and 4]. The three levels of control are defined as well controlled, not well controlled, or very poorly controlled. Based on these categories, the guidelines suggest actions such as maintaining therapy or changing the intensity of therapy by either stepping up or down according to the stepwise approach. Further discussion about changing pharmacotherapy based on the control assessment will be discussed in the May issue of this series.

The frequency at which asthma control is monitored can be based on clinical judgment, although the guidelines recommend an initial interval of two to six weeks for patients initiating therapy or for cases that are determined to be poorly controlled. For more established patients in whom long-term asthma control has been achieved, the interval of follow-up can be extended to a period of one to six months. For patients aged four years or younger, initial follow-up after the initiation of long-term controlled medication should take place at four to six weeks; if no clear benefit is noted from the pharmacotherapy, an alternative diagnosis should be considered.

As with the assessment of asthma severity, the assessment of asthma control is divided into the domains of impairment and risk. Control in the impairment domain is determined by evaluating the same categories of symptoms as with the severity assessment: frequency of daytime symptoms, frequency of nighttime awakenings, frequency of short-acting beta-agonist use other than for prevention of EIB, and the level to which asthma interferes with activities of daily living. As symptoms increase in frequency, the level of control is rated more poorly. A strategy established by the guidelines to remember the designation between well controlled and not well controlled in patients aged five years and older is known as the “Rules of Two.” Patients who have daytime symptoms more than two days per week, nighttime symptoms more than two nights per month, or need rescue inhaler therapy more than two days per week outside of pretreatment for EIB are considered to have asthma that is not well controlled and are candidates for consideration of pharmacotherapy modifications. The Rules of Two has been found to perform as well as a previously validated asthma questionnaire (Asthma Control Test [ACT]) in identifying patients with asthma that is not well controlled.

In patients aged five years and older, spirometry can aid in the assessment of control. In patients aged 12 years and older, there is also the option of using a validated questionnaire to assess asthma control. One of the more commonly used questionnaires is the aforementioned ACT. The ACT is a validated, five-item questionnaire that asks a patient to rate his or her asthma symptoms and use of rescue inhaler over the previous four weeks. Each question contributes to the overall score, which can range from five to 20. A total score of 16 to 19 indicates the asthma is not well controlled and a score of 15 or lower indicates the asthma is very poorly controlled. An ACT score of 20 or more indicates good asthma control. Although the NAEPP EPR-3 guidelines do not specifically suggest the use of a questionnaire to aid in asthma control assessment in children aged younger than 12 years, the Children’s Asthma Control Test (C-ACT) has been validated in children aged four to 11 years. The C-ACT is a seven-item questionnaire with the first four questions directed to the child regarding his or her asthma symptoms and impairment of daily living. The last three questions are directed to the parent/caretaker regarding his or her perception of the child’s asthma symptom frequency. A total score of zero to 27 is possible, with a score of 19 or less suggesting a lack of asthma control. Although
the ACT and C-ACT are convenient tools, neither incorporates assessment of the risk domain, which should also be considered when determining asthma control.

Assessment of the risk domain when determining asthma control is similar to the assessment used when determining asthma severity. Central to all age groups is the frequency of asthma exacerbations in the previous year, as the occurrence of two or more exacerbations requiring systemic corticosteroids within this time period indicates uncontrolled asthma. After the clinician assesses the domains of impairment and risk, the level of asthma control that corresponds with the lowest level of control across both domains should be assigned. For example, if a 23-year-old patient reports daytime symptoms three days per week, no nighttime awakenings, and no exacerbations in the previous year, the patient’s asthma would be classified as not well controlled.

If a patient’s asthma is determined to be uncontrolled according to the control assessment, the pharmacist should take the time to ask the patient or his or her caregiver about inhaler technique, medication adherence, and the influence of environmental triggers. If these factors are thought to contribute to the lack of asthma control, they should be addressed before therapy is stepped up. If none of these factors is identified, clinicians should consider stepping up therapy according to the age-based stepwise approach. A discussion of environmental factors and their role in asthma management is presented below; a discussion of inhaler technique will be included in the August issue of this series and adherence to therapy will be addressed in the May issue of this series.

Nonpharmacologic interventions

Nonpharmacologic interventions are an important part of the overall approach to the management of asthma. Asthma control and symptom severity are influenced in part by exposure to environmental triggers to which a patient is sensitive. Patient education regarding such triggers and how to best avoid or mitigate exposure to triggers is paramount to proper asthma management. Reducing exposure to triggers can reduce airway inflammation, symptoms, and subsequently the medications needed for asthma control.2 Pharmacists are encouraged to screen all asthmatic patients for possible exposure to inhaled allergens, with a particular emphasis on indoor perennial allergens.2 Food allergens are rarely a trigger associated with asthma. In patients who may have sensitivity, allergy skin testing along with the medical history of the patient can be used to determine which specific allergens are linked to the patient’s symptoms. Patients with a clear relationship between asthma symptoms and exposure to inhaled allergens may benefit from immunotherapy, especially in the setting of difficult to control asthma despite the optimization of pharmacotherapy, adherence, and technique. Examples of common inhaled allergens include animal dander, waste products of dust mites, waste products, saliva, and bodies of cockroaches, indoor molds, and outdoor allergens including tree, grass, and weed pollen and molds.2

Once an inhaled allergen has been identified, the patient should reduce exposure through multiple approaches. For example, if a patient is sensitive to dust mites, suggested strategies include encasing mattresses and pillows in allergen-impermeable cases and washing them often in hot water (>130 degrees F), removing carpets, reducing indoor humidity, and minimizing exposure to stuffed animals. Keeping animals outdoors or minimizing the rooms in which they stay within the home can reduce exposure to animal dander. When patients are sensitive to dust or animal dander, caution should be exercised when vacuuming in the home, as vacuuming can aerosolize dust and dander, which may precipitate symptom worsening. For indoor molds, keeping humidity low and fixing sources of water leaks can help to reduce spore counts; if mold is found extensively throughout the home, mold abatement may be necessary. Keeping doors and windows closed and minimizing outdoor time can help to reduce exposure to outdoor allergens. Comorbid allergic rhinitis or seasonal allergies should be addressed and properly managed to minimize the interaction between such comorbidities and worsening asthma symptoms and control. Further details on how to avoid additional triggers can be found in the NAEP EPR-3 report which is publicly available.2

Aside from inhaled allergens, there are several inhaled irritants that can precipitate worsening asthma. Examples of inhaled irritants include tobacco smoke, smoke from a fireplace or stove, strong perfumes, or odors and sprays (eg, hairspray, spray paint).2 Avoidance of such irritants is the best strategy for those who are sensitive. Exercise can also serve as a trigger for asthma symptoms. Aside from pretreatment with a rescue inhaler such as albuterol, patients are encouraged to warm up before exercise and to avoid exercise in environments that are cold with low humidity. Covering the mouth or nose with a scarf could be helpful to patients with sensitivity to this climate pattern. Patients may also be sensitive to sulfites that are found in foods such as dried fruits, beer, and wine. Up to 21% of adults and 5% of children have a sensitivity to aspirin that manifests as asthma symptoms.2 In patients with a history of sensitivity to aspirin or any nonsteroidal anti-inflammatory drug, avoidance of future exposure through the selection of appropriate alternative therapies is warranted. Many over-the-counter drugs contain aspirin or other non-steroidal anti-inflammatory products and pharmacists should educate patients on how to screen for these active ingredients in OTC products. Nonselective beta-blockers are another class of medication that may lead to worsening of asthma symptoms or lack of optimal response to a standard dose of an inhaled short-acting beta-agonist used as rescue therapy. The NAEP EPR-3 suggests the avoidance of nonselective beta-blockers, including eye drops, in patients with asthma.2 A recent meta-analysis found that beta-1 selective blocker use in patients with asthma or chronic obstructive pulmonary disease does not adversely affect airflow or increase asthma symptoms.19 In asthmatic patients who would benefit from the use of selective beta-blockers, particularly for disease states in which beta-blockers have a proven mortality benefit such as post-myocardial infarction or systolic heart failure, therapy with these agents should not be withheld. Pharmacists should still continue to monitor such patients for worsening of
**TEST QUESTIONS**

1. Which of the following cell types plays a role in bronchial hyperresponsiveness through release of cytokines?
   - a. Eosinophils
   - b. Dendritic cells
   - c. Neutrophils
   - d. Mast cells

2. Two major factors that influence the development and persistence of asthma are:
   - a. Respiratory infections and airborne allergens
   - b. Recurrent bacterial infection and air pollution
   - c. Respiratory infections and air pollution
   - d. Airborne allergens and recurrent bacterial infection

3. As asthma progresses over time, pathophysiologic changes are consistent with which of the following?
   - a. Decreased mucus secretion
   - b. Airway edema
   - c. Smooth muscle hyperplasia
   - d. B & C

4. The hygiene hypothesis:
   - a. Suggests that a reduction in the exposure to infectious agents has decreased the incidence of asthma and other immune related conditions
   - b. Illustrates how a cytokine imbalance may explain increased asthma prevalence in Westernized countries
   - c. Is based on the idea that the naive immune system is skewed to express the Th-1 phenotype
   - d. Explains the development of adult-onset asthma

5. Which of the following has been shown to influence the development of asthma?
   - a. Obesity
   - b. Tobacco smoke
   - c. Air pollution
   - d. All of the above

6. The most common triad of asthma symptoms includes:
   - a. Cough, bronchitis, dyspepsia
   - b. Wheezing, cough, dyspnea
   - c. Dyspnea, conjunctival inflammation, cough
   - d. Wheezing, cough, sore throat

7. Which of the following is FALSE regarding nocturnal symptoms of asthma?
   - a. Bronchoconstriction is highest between 12 AM and 4 AM, leading to nocturnal symptoms associated with asthma.
   - b. Nocturnal symptoms are caused by an exaggerated response to the normal circadian variation in airflow.
   - c. Nocturnal symptoms have been associated with an increase in inflammation and may indicate uncontrolled disease.
   - d. Pediatric patients tend to have more nighttime symptoms associated with asthma.

8. Nonpulmonary manifestations of asthma include which of the following?
   - a. Conjunctival inflammation
   - b. Transverse crease on the nose
   - c. Eczema
   - d. All of the above

9. Exercise-induced bronchospasm:
   - a. Occurs in patients doing strenuous aerobic exercise
   - b. Presents with symptoms very different from asthma
   - c. May be caused by activities such as walking up a flight of stairs or walking up a steep incline
   - d. Is not attributed to seasonal changes or temperature and humidity of the environment

10. During a severe acute asthma exacerbation, patients experience:
    - a. Regular respiratory rate, difficulty in full sentences, and ability to lie down in a flat position
    - b. Increased respiratory rate, breathlessness while speaking, and pulsus paradoxus
    - c. Increased respiratory rate, ability to talk in full sentences, and ability to lie down in a flat position
    - d. Decreased respiratory rate, profuse diaphoresis, and confusion

11. Assessment of asthma severity is best performed:
    - a. Before the diagnosis of asthma
    - b. Before the start of long-term controller medications
    - c. After the start of long-term controller medications
    - d. After the use of a rescue inhaler

12. The use of spirometry to aid in the assessment of asthma severity is recommended in all but which of the following patient groups?
    - a. Aged four years and younger
    - b. Aged five to 11 years
    - c. Aged 12 years and older
    - d. Spirometry can be used in all age categories

13. FL is a 32-year-old patient who was recently diagnosed with asthma. He reports that he has daytime symptoms three to four days per week and nighttime awakenings two times per month, and he has never had an asthma exacerbation. Based on this information, which level of asthma severity does FL have?
    - a. Intermittent
    - b. Mild persistent
    - c. Moderate persistent
    - d. Severe persistent

14. Asthma is not a definitive diagnosis in patients of this age category, and often a trial of maintenance medications is used to determine whether the symptoms are likely to be asthma related?
    - a. Aged four years and younger
    - b. Aged five to 11 years
    - c. Aged 12 years and older
    - d. All of the above

15. Which of the following is used to assess asthma control within the impairment domain?
    - a. Frequency of daytime symptoms
    - b. Frequency of asthma exacerbations
    - c. Adherence to medications
    - d. Status of influenza vaccination

16. Which of the following is a validated questionnaire that can be used to assess asthma control in patients aged 12 years and older?
    - a. C-ACT
    - b. CHAIDS-VASc
    - c. Asthma Control Test
    - d. Peak expiratory flow

17. KT is a six-year-old girl who has been started on a maintenance regimen for her asthma. After about four weeks of therapy, KT continues to have nighttime symptoms two to three times per month and daytime symptoms once per week, and she has not had any asthma exacerbations. How would you rate her level of asthma control?
    - a. Well controlled
    - b. Not well controlled
    - c. Very poorly controlled

18. How long after a patient begins initial asthma treatment should their control be assessed?
    - a. One week
    - b. Four weeks
    - c. Eight weeks
    - d. 12 weeks

19. In a patient with asthma determined to be uncontrolled, which of the following factors may be contributing to the lack of control?
    - a. Adherence to medications
    - b. Technique with inhalers
    - c. Environmental triggers
    - d. All of the above

20. The NAEPP EPR-3 guidelines emphasize evaluation of an asthmatic patient’s sensitivity to which of the following possible triggers?
    - a. Inhaled perennial allergens
    - b. Food sensitivities
    - c. Inhaled irritants
    - d. Sulfites
asthma symptoms as a precaution, especially as the dose of selective beta-blockers is increased and the selectivity for the beta-1 receptors decreases.

Viral respiratory infections are an important trigger that can lead to asthma exacerbations, particularly in children aged less than 10 years.2 Rhinovirus, RSV, and influenza have been implicated as viral triggers of asthma. Not only can asthma symptoms be exacerbated during the infection, these effects may persist for days or weeks after the viral infection has resolved. The Centers for Disease Control and Prevention (CDC) states that asthmatic adults and children aged six months and older should receive an annual influenza vaccination, as patients with a chronic lung disease have been identified as a special population at higher risk of complications from influenza.20 Of note, children aged two to four years who have asthma or who have experienced wheezing in the previous 12 months should not receive the live attenuated influenza vaccine. In all patients with asthma, regardless of age, there may be increased risk of wheezing after administration of the live attenuated influenza vaccine.20 Infants and toddlers receive a series of pneumococcal vaccinations per standard immunization practices in the United States, regardless if they have asthma. If a child is 24 months of age or older and was not previously immunized against pneumococcus and has asthma treated with high-dose oral steroids, the CDC recommends two doses of PCV13 with a minimal interval of eight weeks between doses.21 Pharmacists can play an important role in identifying and subsequently immunizing patients with asthma, consistent with guideline recommendations.

Two additional comorbid conditions are implicated in optimizing asthma control: gastroesophageal reflux disease (GERD) and obstructive sleep apnea. GERD and asthma are commonly found to coexist in patients, although the relationship between changes in asthma symptoms and control with changes in GERD symptoms is not clear. It is reasonable to treat GERD, especially in asthmatic patients with nocturnal symptoms and in asthmatic patients with GERD symptoms whose asthma is poorly controlled despite optimal pharmacotherapy, adherence, and technique. Patients with unstable asthma who are also obese may have an underlying component of obstructive sleep apnea; identification and management of this condition may improve asthma symptoms and control.2

Conclusion
Given the millions of patients who are affected by asthma in the United States, there is a large opportunity for pharmacists to become involved in asthma patient care. Evidence-based guidelines clearly delineate the steps that should be used to properly assess the severity and control of asthma as part of the process of care. The next article in this series will discuss the medications used in asthma management and will review the stepwise approach for medication selection and alteration based on control assessment. •

References are available online at www.drugtopics.com/cpe.

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