This discussion of asthma management will consider issues related to both diagnosis and treatment of this extremely common disease, which affects approximately 5-10 percent of the population. Many guidelines have been developed to assist the physician with management of patients with asthma; this presentation will focus on the latest guidelines (the 3rd Expert Panel Report) issued in 2007 by the National Asthma Education and Prevention Program, sponsored by the National Institutes of Health in the United States. These guidelines are available on the Internet at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

DIAGNOSIS

Asthma is characterized by partially or fully reversible episodes of airflow obstruction and airway hyperresponsiveness. Although the diagnosis is often made clinically, it is ideally confirmed by documenting episodic airflow obstruction, as measured by changes in FEV₁. If FEV₁ is abnormal at the time of measurement, there should be at least partial bronchodilator responsiveness, as seen by at least a 12% and a 200 mL increase in FEV₁ from baseline following inhalation of a short-acting beta-agonist. Alternatively, if the baseline FEV₁ is normal, airway hyperresponsiveness can be demonstrated by a bronchoprovocation challenge with methacholine. A positive methacholine test is defined by a PC₂₀<8 mg/mL, i.e. the concentration of methacholine needed to produce a fall in FEV₁ of 20% is 8 mg/mL or less. Although a methacholine challenge test is sensitive for diagnosing asthma, it is not specific. Therefore, a negative test effectively rules out asthma, but a positive test can be seen in other circumstances and therefore does not definitively confirm the diagnosis.

DISORDERS MIMICKING ASTHMA

When making the diagnosis of asthma, it is important to remember that other clinical disorders can resemble asthma. Both postnasal drip and gastroesophageal reflux can result in upper airway irritation and inflammation mimicking asthma, but both of these problems can also exacerbate pre-existing asthma. Another important condition that often can resemble asthma is paradoxical vocal cord motion. In this disorder, the vocal cords adduct (rather than abduct) during inspiration, often resulting in inspiratory stridor. An additional clue to the patient presenting with an acute episode of paradoxical vocal cord motion is a normal oxygen saturation or normal \( P_{O2} \), whereas oxygenation is often abnormal in patients with an acute exacerbation of asthma. Congestive heart failure, resulting in airway narrowing from peribronchial edema, can also mimic asthma and is often referred to as “cardiac asthma.” Cystic fibrosis and alpha-1 antitrypsin deficiency are two genetic disorders that can produce airway obstruction and be misdiagnosed as asthma. Finally, following a viral upper respiratory tract infection, many patients experience cough and airway hyperreactivity that is transient but can be mistaken for asthma.

DISORDERS ASSOCIATED WITH ASTHMA

At the same time there are disorders that can mimic asthma, there are also individuals in whom asthma is either associated with, or represents a component of, another clinical problem. For example, in Churg-Strauss syndrome (allergic angiitis with granulomatosis), patients have asthma accompanied by a systemic vasculitis and often pulmonary infiltrates. In allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity response to airway colonization with Aspergillus typically complicates and worsens pre-existing asthma. Potential clues to ABPA include the development of pulmonary infiltrates or proximal bronchiectasis in a patient with pre-existing asthma that has often become more difficult to manage. Other patients with asthma may have an entity that has been called either “triad asthma” or “Samter’s syndrome,” in which asthma is associated with nasal polyposis and aspirin sensitivity. Finally, an important diagnosis to recognize, largely because it is readily treatable with systemic steroids, is chronic eosinophilic pneumonia. Patients with chronic eosinophilic pneumonia often have underlying asthma, and a clue to the diagnosis can be provided by the finding on chest radiograph of peripheral pulmonary infiltrates with central sparing (often described as the “photographic negative” of pulmonary edema).

ASTHMA SEVERITY CLASSIFICATION

The asthma severity classification outlined by the National Asthma Education and Prevention Program is intended to categorize the intensity of the patient’s disease at the time of presentation. This assessment of asthma severity is a guide to the initiation of therapy. In contrast, subsequent management is based upon the adequacy
of the patient's control, which represents the degree to which the manifestations of asthma are minimized by therapy and the goals of therapy are met. Assessing and monitoring how well the asthma is controlled then guides the subsequent adjustment of therapy.

The classification of asthma severity at initial presentation is shown below:

### Classifying Asthma Severity*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Day Symptoms</th>
<th>Night Symptoms</th>
<th>FEV1</th>
<th>Interference with activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>&lt;2 days per week</td>
<td>&lt;2 nights per month</td>
<td>&gt;80%</td>
<td>None</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>&gt;2 per week, &lt;1 per day</td>
<td>3-4 nights per month</td>
<td>&gt;80%</td>
<td>Minor limitation</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily</td>
<td>&gt;1 night per week</td>
<td>&gt;60% - &lt;80%</td>
<td>Some limitation</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual</td>
<td>Often nightly</td>
<td>≤60%</td>
<td>Extremely limited</td>
</tr>
</tbody>
</table>

*Used for patients not taking long-term control medications (From NAEPP, 2007)

### Adjusting Asthma Control

<table>
<thead>
<tr>
<th>Level of Control</th>
<th>Symptoms</th>
<th>Night Awakening</th>
<th>FEV1 or PEFR*</th>
<th>Interference with activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well controlled</td>
<td>≤2 days per week</td>
<td>≤2 nights per month</td>
<td>&gt;80%</td>
<td>None</td>
</tr>
<tr>
<td>Not well controlled</td>
<td>&gt;2 days per week</td>
<td>1-3 nights per week</td>
<td>60-80%</td>
<td>Some limitation</td>
</tr>
<tr>
<td>Very poorly controlled</td>
<td>Daily</td>
<td>&gt;4 nights per week</td>
<td>&lt;60%</td>
<td>Extremely limited</td>
</tr>
</tbody>
</table>

Well controlled: continue current rx.; consider step down if controlled ≥3 months
Not well controlled: step up by 1 step
Very poorly controlled: consider short course of oral steroids; step up 1-2 steps

*Predicted or personal best (From NAEPP, 2007)

Using the guidelines in the above table, the clinician can adjust the medication regimen according to the step-wise approach outlined in the following table.

### Step-Based Therapy of Asthma

<table>
<thead>
<tr>
<th>Preferred Medication</th>
<th>Treatment Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA pm</td>
<td>1  2  3  4  5  6</td>
</tr>
<tr>
<td>ICS</td>
<td>✓  ✓  ✓  ✓  ✓  ✓</td>
</tr>
<tr>
<td>LABA</td>
<td>✓  ✓  ✓  ✓  ✓  ✓</td>
</tr>
<tr>
<td>Oral CS</td>
<td>✓  ✓  ✓  ✓  ✓  ✓</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Consider Consider</td>
</tr>
</tbody>
</table>

SABA = short-acting β-agonist; LABA = long-acting β-agonist; ICS = inhaled corticosteroids; Oral CS = oral corticosteroids; LD = low-dose; MD = medium-dose; HD = high-dose

As can be seen, with the mildest disease, as would be seen with a patient whose asthma initially falls into the category of intermittent disease, therapy would start with a short-acting beta-agonist. The step-wise approach to therapy, if the disease is not well controlled at each step, is to progressively escalate therapy (as noted by the circled items) by adding a low-dose inhaled corticosteroid, then adding a long-acting inhaled beta-agonist, then increasing to moderate-dose inhaled steroids, then high-dose inhaled steroids, and finally adding oral corticosteroids. With more severe or poorly controlled disease, one could consider adding anti-IgE therapy with omalizumab.

As already mentioned, establishing a self-management plan with the patient is an important component of therapy. These plans, which provide guidance to the patient about what to do in the face of escalating symptoms or decreasing pulmonary function, have been shown to reduce hospitalizations and emergency room visits and to improve pulmonary function.

**GENERAL PRINCIPLES OF ASTHMA TREATMENT**

The standard way to treat asthma is to use a step-wise approach, based upon the severity of the disease and the effectiveness of the therapy at each step of the management process. Perhaps the most important overall principle is that anti-inflammatory controller medication, typically an inhaled steroid, should be used for any level of severity of asthma beyond just intermittent disease.

Self-management plans are also particularly important for the patient with asthma, so that he or she understands what to do in the event of increasing symptoms or decreasing expiratory flow rates (if the patient is self-monitoring flow rates with a peak expiratory flow meter). Patients should also be instructed on the technique for using an inhaler as well as the technique for using a peak expiratory flow meter. Although instruction about technique is important, it is not sufficient, as patients should be observed using their inhaler and, if applicable, their peak expiratory flow meter.

### ADJUSTING ASTHMA MEDICATIONS ACCORDING TO ADEQUACY OF CONTROL

Once a patient is on therapy, the adequacy of asthma control is based upon frequency of symptoms, frequency of nocturnal awakening from asthma, measurement of expiratory airflow (either FEV₁ or peak expiratory flow rate), and the degree to which asthma interferes with the patient's activity. The specific categories are shown in the following table, along with the implications for management:
Because it is often difficult for patients to remember what they hear at the time of an office visit, it is important that the action plan be written down for the patient. At present, there is no clear evidence about whether the patient’s self-management plan should be based primarily on symptoms or on the results of peak expiratory flow rate monitoring. However, there is a consensus that peak expiratory flow rate monitoring should be done by patients whose asthma falls into the categories of either moderate or severe persistent asthma.

**MISCELLANEOUS POINTS AND RECENT ARTICLES ABOUT TREATMENT**

Several other points about treatment are worth stressing, including some points taken from recent articles in the literature. Although this discussion has focused on issues relating to the ongoing management of patients with asthma, it is worthwhile to mention a couple of items relating to management of asthmatic patients during an acute exacerbation. First, it is well recognized that adding antibiotics to standard care does not improve outcomes in acute exacerbations of asthma. Besides adding to the cost of care, the use of antibiotics in acute exacerbations of asthma can lead to unwanted side effects for the patient and can contribute to increasing antibiotic resistance. Another topic that often comes up when discussing management of acute exacerbations of asthma is the issue of systemic steroid dosage. Systemic steroids clearly play an important role in the acute management of asthma, but dosages have varied enormously over the years. Despite the frequent use of very high dose steroids in acute exacerbations, a Cochrane meta-analysis has shown that there is no advantage to high dose (>360 mg/24 hrs.) over low dose (<80 mg/24 hrs.) methylprednisolone in the management of acute asthma exacerbations (Cochrane Database Syst Rev 2000; 2:CD001740).

For some patients, leukotriene antagonists such as montelukast have become an option for use as a controller medication. Interestingly, the response to leukotriene antagonists can vary considerably from patient to patient. The underlying reason for this variability may relate to differences in genetic expression of 5-lipoxygenase in individual patients, with consequent differences in importance in the role of leukotrienes in a particular patient’s asthmatic phenotype.

As mentioned earlier, the consequences of gastroesophageal reflux can sometimes mimic asthma, and it has been thought that reflux can also lead to worsening asthma control. However, despite the common presence of asymptomatic gastroesophageal reflux in patients with poorly controlled asthma, treatment with proton pump inhibitors does not improve asthma control in such patients in the absence of symptoms of reflux disease (N Engl J Med 2009; 360:1487).

Potential newer treatments for asthma are based on a mechanism-based approach. Just as anti-IgE therapy is targeting IgE as an important mediator in allergic asthma, another potential mechanistic approach focuses on chemokines believed to be important in the allergic response, such as interleukin-5 (IL-5). In a recent study, mepolizumab, an investigational monoclonal antibody against interleukin-5, decreased frequency of exacerbations in patients with refractory eosinophilic asthma and recurrent severe exacerbations (N Engl J Med 2009; 360:973 and 985). Whether this approach will ultimately prove fruitful in the management of asthma remains to be seen.

**THE LONG-ACTING BETA-AGONIST CONTROVERSY**

For several years, a question raised in the asthma literature has been whether long-acting beta-agonists paradoxically might worsen disease control, and whether they are associated with increased asthma mortality. For example, in one meta-analysis, long-acting beta-agonists were associated with increased exacerbations requiring hospitalization and increased risk for asthma-related deaths (Ann Intern Med. 2006; 144:904-12).

However, rather than the long-acting beta-agonists themselves being responsible for the above findings, another interpretation is that absence of a controller medication such as inhaled corticosteroids was responsible, if the long-acting beta-agonists were used instead of, not in addition to, a controller medication. Supporting this hypothesis are other meta-analyses that have demonstrated no increase in risk associated with use of long-acting beta-agonists in patients who are taking inhaled steroids as part of their regimen (Cochrane Database Syst Rev 2009: CD006922 and Am J Respir Crit Care Med 2008; 178:1009). A logical conclusion is that long-acting beta-agonists should not be used in asthma in the absence of a controller medication such as inhaled corticosteroids.

**WHAT IS THE ROLE OF ANTI-IgE THERAPY?**

Omalizumab is a recombinant humanized IgG1 monoclonal antibody against IgE. A Cochrane review in 2006 found that omalizumab used in asthmatic patients decreases the need for inhaled steroids and decreases the frequency of exacerbations. However, the overall clinical value of being able to reduce the inhaled steroid dose is not clear. In addition, the value of omalizumab relative to other treatments, such as leukotriene inhibitors, is unknown. There is a potential risk of anaphylaxis with anti-IgE therapy, though this is a rare complication. Because omalizumab is a very expensive medication, with a cost of $4000-20,000 US dollars per year, its utility and indications remain unclear (N Engl J Med. 2006; 354:2689).

**MEASUREMENT OF EXHALED NITRIC OXIDE (NO): AN ADVANCE IN DIAGNOSIS?**

There has been recent interest in the use of measuring and monitoring exhaled nitric oxide (NO) as a marker of airway inflammation. Exhaled NO correlates with eosinophilic airway inflammation, as is seen in asthma. A question of interest is whether measurement of exhaled NO could guide the use of inhaled corticosteroids. To date, conflicting results have been
obtained about this question. For example, one study showed that monitoring asthmatic patients with NO as a guide to therapy can result in significantly reduced maintenance doses of inhaled steroids without any compromise in the patient’s control (N Engl J Med. 2005; 352:2163). In contrast, other negative studies found that use of exhaled NO did not result in decreased doses of inhaled steroids or in improved asthma control (Am J Respir Crit Care Med 2007; 176:231; Lancet 2008; 372:1065).

CONCLUSIONS

In summary, a number of points can be taken home from the above discussion:

- Spirometric demonstration of reversible airflow obstruction is key to the diagnosis
- It is important to be aware of other disorders that can mimic or complicate asthma
- The stepwise approach to managing asthma is continually being refined
- Newer methods of monitoring airway inflammation and treating based on disease mechanisms may become clinically applicable in the future