ASTHMA MANAGEMENT: OPTIMIZING TREATMENT FOR A DISEASE OF VARIABLE INTENSITY

David Stempel, MD *

ABSTRACT

National and international asthma management guidelines advocate a stepwise approach to asthma treatment based on severity-based classification of patients. Although this approach serves an important purpose in guiding therapeutic decision making and decreasing unnecessary variation in care, it has limitations—particularly with respect to the management of what the guidelines define as mild and moderate persistent asthma. The diagnosis of persistent asthma is confounded both by the variable pattern of asthma severity and by patients' failure to recognize and report symptoms, with a consequent underassessment of symptom severity by the healthcare provider. This paper reviews the data supporting these points and discusses the implications for the management of asthma. (Advanced Studies in Medicine. 2002;2(14):504-510)

Asthma management guidelines, including those of the National Asthma Education and Prevention Program (NAEPP), classify asthma according to severity. Asthma severity is determined by the frequency of symptoms, history of exacerbations, and the results of pulmonary function tests. The most severe finding is used as the basis for classification and initial stepwise therapy in the management of the disease. The guidelines have no specific modification for previous or current controller therapy. Although severity-based stratification of patients serves an important purpose in guiding therapeutic decision making, evidence suggests significant limitations to this approach—particularly in attempts to distinguish patients with mild and moderate persistent asthma. These 2 categories often overlap in patients with asthma. Normal lung function may cause a physician to not question a patient about possible symptoms and therefore underclassify the patient's asthma severity. Furthermore, patients tend to underrecognize the presence and severity of symptoms and therefore do not report their symptoms to their caregivers. Finally, asthma severity is variable and may be mild in intensity unless the patient is exposed to allergens or develops a respiratory infection. These isolated flares are accounted for in the guidelines for young children (<5 years) but not in the NAEPP recommendations for adolescents and adults. One of the goals of asthma treatment is the prevention of exacerbations. Proper controller therapy is needed to prevent exacerbations. Proper diagnosis is therefore needed to ensure that the appropriate level of medication is prescribed, "Because asthma is a chronic disease characterized by differing frequencies of daily symptoms, exacerbations, and remissions, characterizing disease severity is problematic."

* Associate Clinical Professor, University of Washington, Seattle, WA.
Asthma-Severity Classification: NAEPP Guidelines

The NAEPP defines asthma severity by the frequency and severity of symptoms and the results of pulmonary function tests (Table). The particular asthma severity that is assigned is determined by the most severe finding. Classifying asthma by severity and making treatment decisions on the basis of severity classification is problematic because asthma is a variable disease—both on a day-to-day basis and from season to season—rather than a static entity. Accordingly, a patient’s asthma may shift from one severity category to another from day to day and over the long term. Furthermore, the various criteria used to determine asthma severity do not yield consistent categorization.

In one study of data from 1429 patients participating in 5 controlled clinical trials, only 24% of patients were classified as having severe asthma based on forced expiratory volume in 1 second (FEV₁), whereas 55% of patients were classified as having severe asthma based on nighttime wheezing. This dissociation between results of pulmonary function tests and nighttime symptom scores may have occurred because pulmonary function tests are almost always performed during the daytime, when patients are typically less symptomatic than they are at nighttime. During the nighttime hours, mediator release is highest and catecholamine and glucocorticoid production is lowest, reflecting changes that may increase asthma severity. In addition, seasonal variation in allergen exposure and endemic or epidemic respiratory illnesses may alter the frequency and severity of symptoms. Regardless of the reason for the discrepancy between pulmonary function test results and symptom ratings, these considerations highlight the importance of considering all of the patient’s symptoms as well as results of pulmonary function tests in assessing asthma severity.

Mild Asthma May Not Be Mild

These shortcomings of severity-based schemes become particularly apparent in attempts to categorize and manage asthma that appears to be mild or mild intermittent. Several lines of evidence suggest that asthma meeting specific severity criteria for being mild may not be mild regarding health consequences. Substantial numbers of patients with mild asthma experience frequent exacerbations and are even at risk for death from asthma. In a retrospective study of

<table>
<thead>
<tr>
<th>Asthma Severity</th>
<th>Symptoms</th>
<th>Nocturnal Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
<td>Symptoms ≤2 times/week</td>
<td>≤2 times/month</td>
<td>FEV₁ or PEFR, &gt;80% of predicted PEFR variability, &lt;20%</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic and normal PEFR between exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations brief (from a few hours to a few days); intensity may vary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild persistent</td>
<td>Symptoms &gt;2 times/week</td>
<td>&gt;2 times/month</td>
<td>FEV₁ or PEFR, &gt;80% of predicted PEFR variability, 20% to 30%</td>
</tr>
<tr>
<td></td>
<td>but &lt;1 time/day Exacerbations may affect activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily symptoms</td>
<td>&gt;1 time/week</td>
<td>FEV₁ or PEFR, &gt;60% to &lt;80% of predicted PEFR variability, &gt;30%</td>
</tr>
<tr>
<td></td>
<td>Daily use of inhaled short-acting beta-2 agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations affect activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations ≥2 times/week; may last days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual symptoms</td>
<td>Frequent</td>
<td>FEV₁ or PEFR, ≤60% of predicted PEFR variability, &gt;30%</td>
</tr>
<tr>
<td></td>
<td>Limited physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent exacerbations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in 1 second; PEFR = peak expiratory flow rate.
13,842 children with asthma observed over a 15-year period, 1 in 5 patients with an FEV₁ of 100% to 120% of predicted had an asthma exacerbation over a 1-year period (Figure 1). In another study investigating deaths of all patients age 20 years or younger who died from asthma in the Australian State of Victoria, 33% of the 51 patients whose deaths were attributed to asthma over a 3-year period were considered to have had a history of trivial or mild asthma. It is unclear whether these children had mild asthma or if their disease severity was under-recognized. Asthma deaths were judged to have been preventable in 39% of cases. The most common preventable reasons for death were inadequate assessment and inadequate therapy, which were judged to have accounted for 68% of preventable deaths. Spirometry to assess disease severity had been performed in only 18 of the 50 patients capable of spirometry during the year before their death. Bronchodilators were the only therapy in one half of the patients, and most patients reported that their activity was not limited by their asthma. A similar pattern of results was observed in a study of deaths in residents of Wales (age, newborn to 65 years). Preventable factors were judged to have contributed to 46 of the 52 deaths. The most common failure in medical care was inadequate treatment for the severity of the disease. The pattern of results from these investigations of asthma deaths suggests that, rather than dying from mild asthma, these patients died from asthma that was severe but was under-reported, underdiagnosed, and therefore undertreated.

**APPROPRIATE ADJUSTMENT TO DISEASE-SEVERITY CLASSIFICATION TO ENHANCE ACHIEVEMENT OF ASTHMA THERAPY GOALS**

According to the NAEPP guidelines, mild intermittent asthma does not warrant daily controller therapy. The preferred treatment for mild persistent asthma is low-dose inhaled corticosteroids; for moderate persistent asthma, the preferred treatment is the combination of an inhaled corticosteroid and an inhaled long-acting beta-2 agonist. Because of the variability of asthma, these disease classifications are difficult to distinguish based on clinical criteria. The intermittent nature of exacerbations, the effect of therapy on classification, and the underreporting of symptoms may make the distinctions among severity levels unclear. Objective measurement of lung function is an essential means of assessing disease severity but also has limitations that require attention to clinical parameters at the time of testing. Adult patients are often evaluated during the daytime hours, when their lung function is typically higher compared with the evening and nighttime, when asthma exacerbations are more common. Lung function is often assessed when patients are stable and not during flares. In addition, there is a need to redefine normal predictive values in pediatric patients because many children have higher than normal levels and remain chronically symptomatic.

**BIOPSY STUDIES**

Biopsy studies suggest that the distinctions among asthma-severity levels are easily blurred. In one ran-
domized, double-blind, parallel-group trial, patients with normal lung function (morning peak expiratory flow rate [PEFR], 94%; evening PEFR, 99%; percent of predicted FEV1, 89%) who had been diagnosed with asthma 2 to 12 months before initiation of the study received controller therapy with either budesonide, 600 µg twice daily (n = 7), or terbutaline, 375 µg twice daily (n = 7).8 One of the most impressive results of this study was that the baseline biopsy findings demonstrated significant evidence of airway inflammation with disrupted ciliated epithelium, eosinophilic infiltration, and subbasement membrane collagen deposition. After treatment with inhaled corticosteroids, but not terbutaline, the newly diagnosed asthmatics (normal lung function notwithstanding) had significant improvement in biopsy findings. Epithelial cell architecture returned to normal and eosinophils were reduced in both the epithelium and the lamina propria from bronchial biopsy specimens after 3 months of budesonide treatment (Figure 2).

A similar pattern of results was obtained in a double-blind parallel-group study of the effects of inhaled fluticasone propionate, 250 µg twice daily, or placebo for 6 weeks in nonsmoking patients with asthma who required only beta-2 agonists to control their symptoms.9 These patients had normal lung function (mean FEV1, 103% of predicted) before beginning therapy. Compared with patients treated with placebo, those treated with fluticasone propionate had significant decreases in the number of cells expressing intracellular adhesion molecule-1, tryptase level in bronchoalveolar lavage, numbers of eosinophils and mast cells in the lamina propria, and thickness of the basement membrane. The authors concluded that short-term, low-dose treatment with fluticasone propionate may modify airway remodeling in mild asthma.

CLINICAL STUDIES

The effects of controller therapy in patients with near-normal lung function were assessed in the Childhood Asthma Management Program (CAMP) study, in which 1041 children aged 5 to 12 years were randomized to receive budesonide, 200 µg twice daily, nedocromil, 8 mg twice daily, or placebo for 4 to 6 years.10 All patients had mild to moderate asthma as defined by symptoms, albuterol use, or daily use of asthma medications, although the mean prebronchodilator FEV1 was greater than 93% of predicted. Even in these patients with normal lung function, budesonide improved airway hyperresponsiveness and resulted in better control of asthma compared with placebo or nedocromil. Compared with patients taking placebo, patients treated with budesonide had significantly improved airway responsiveness to methacholine, 43% fewer hospitalizations, 45% fewer urgent-care visits, and 43% fewer courses of prednisone. The patients treated with inhaled corticosteroids had a greater reduction in symptoms and need for albuterol compared with those taking placebo. The benefits of nedocromil compared with placebo were less conclusive. Thus, daily controller therapy with inhaled corticosteroids improved symptoms and measures of lung function and reduced healthcare resource utilization among these patients with near-normal lung function at baseline.

Similar results were observed by O’Byrne et al in the OPTIMA (Oxis and Pulmicort Turbuhaler in the Management of Asthma) trial.11 Patients with mild
asthma who, at baseline, were either corticosteroid free (Group A; n = 698) or had received low doses of an inhaled corticosteroid and had relatively mild symptoms (Group B; n = 1272) were randomly assigned to treatment as shown in Figure 3.

The results of OPTIMA show that, in Group A, budesonide significantly reduced the risk of severe exacerbation by 60% and reduced poorly controlled asthma days by 48%. The rate of severe exacerbations was likewise significantly reduced with budesonide compared with placebo (Figure 4). [Severe exacerbation was defined as the need for oral corticosteroids, hospital admission, emergency treatment for worsening asthma, or a decrease in morning PEFR greater than 25% from baseline on 2 consecutive days. Poorly controlled asthma was defined as morning PEFR more than 20% below the baseline value, use of rescue medication more than twice as often as at baseline, or awakenings because of asthma.] One third of patients in the placebo group had a severe exacerbation during the 1-year study and had poorly controlled asthma on 14% of days—a result that underscores the importance of anti-inflammatory therapy for patients with mild asthma. Patients treated with the combination of inhaled budesonide and formoterol had a 2-fold greater improvement in PEFR compared with those taking placebo or budesonide alone.

In Group B, adding formoterol reduced the risk of severe exacerbation by 43% and reduced poorly controlled asthma days by 30% compared with budesonide alone. The rate per patient per year of severe exacerbations was 0.92 with budesonide, 100 µg twice daily; 0.96 with budesonide, 200 µg twice daily; 0.56 with budesonide, 100 µg plus formoterol twice daily; and 0.36 with budesonide, 200 µg plus formoterol twice daily (Figure 4). This study demonstrates the importance of appropriate treatment in reducing the frequency of exacerbations, improving lung function, and decreasing symptoms. This study also illustrates the difficulty with disease stratification based on the guidelines. Of note, the patients in both arms of the study had normal lung function. Group A patients were classified as "mild" and were not on inhaled corticosteroid therapy. Group B patients were also classified as "mild" asthmatics with normal lung function that was likely a result of their low-dose inhaled corticosteroid treatment. With these criteria, there is no clear consensus among physicians whether these patients have mild persistent or moderate persistent asthma; the guidelines have difficulty adjusting for previous controller medications. Underestimated disease severity and undertreatment would place these patients at risk for a greater number of exacerbations.

Similar results have been obtained with other corticosteroid-bronchodilator combinations used in the treatment of mild asthma. The combination of fluticasone propionate, 250 µg twice daily, and salmeterol, 50 µg twice daily, for 4 weeks as initial treatment for patients with mild to moderate asthma (n = 127) was associated with a 13% increase in morning PEFR, a 12.5% increase in FEV₁, and a 1.9-puff reduction in
rescue medication use compared with baseline in an open-label study.12

**CONCLUSIONS: EFFECT OF CONTROLLER THERAPY IN MILD ASTHMA**

Considered together, the biopsy data and the clinical studies show that patients with mild persistent asthma have airway damage and are at risk for asthma exacerbations. These findings also show that pharmacotherapy with inhaled corticosteroids or the combination of inhaled corticosteroids and bronchodilators can significantly improve airway integrity, symptoms, and lung function. These improvements are observed even in patients with normal lung function and with asthma that meets NAEPP criteria for being mild and intermittent. These findings reinforce the points that the patient's symptoms must be fully assessed and combined with pulmonary function to appropriately classify asthma severity. Furthermore, previous or concurrent controller therapy needs to be added to the equation when determining proper disease severity ranking. This data is needed to determine the appropriate course of treatment. Normal lung function should not be a reason to delay treatment in symptomatic patients. Likewise, the absence of symptoms reported by the patient should not be used as a basis for assigning asthma severity without obtaining normal lung function measures because patients and family frequently underreport the severity of symptoms. Some of these points are also illustrated in an actual case study of a patient who may be typically encountered in an asthma clinic or primary care practice (see page 511).

**REFERENCES**


