ABSTRACT

The National Heart, Lung, and Blood Institute's 1997 National Asthma Education and Prevention Program (NAEPP) classifies asthma severity on the basis of lung function and symptoms, and most clinicians use either or both of these measures to assess patients. Severity-based stratification of patients provides a useful framework for therapeutic decision making, but this approach should not be adopted without an understanding of its delimitations and challenges. Accurate assessment of asthma severity is crucial in ensuring the patient's health and well-being. The consequences of misappraisal of patients' clinical status include unnecessary prescription of medication when severity is overestimated and failure to intervene with resulting deterioration of asthma control—possibly culminating in death—when severity is underestimated. This review reveals that applying the NAEPP's severity-based classification of patients with asthma in clinical practice can be challenging, particularly in the care of patients at the mild end of the asthma severity continuum. The variable nature of asthma, the poor concordance among measures of asthma severity, and patients' tendency to underreport their asthma symptoms can contribute to inaccurate severity assessments, which can lead to inappropriate therapeutic choices, such as undertreatment. Undertreatment of the patient with mild asthma can be as dangerous as undertreatment of patients with more severe disease. By keeping the challenges associated with severity-based stratification of patients top-of-mind, healthcare providers may be better able to overcome them in clinical practice.

NAEPP Classification of Asthma Severity

The NAEPP guidelines for the diagnosis and management of asthma set forth a severity-based classification scheme to aid in patient management (Table 1). Severity categories (mild intermittent, mild persistent, moderate persistent, and severe persistent) are determined on the basis of symptoms and the objective lung function measures of forced expiratory volume in 1 second (FEV₁) or peak expiratory flow (PEF); pharmacotherapeutic intervention is tailored to asthma severity.

The NAEPP guidelines emphasize that this severity-based stratification of patients and the corresponding recommendations for pharmacotherapy are intended to be general guiding principles for therapeutic decision making rather than prescriptions for management of the individual patient. The guidelines should not supplant intervention efforts tailored to the individual patient’s specific needs. Flexibility in interpretation and implementation of the guidelines is needed in order to address the challenges of applying severity-based stratification of patients to treatment choices in clinical practice.

Challenge 1: Severity Classification Varies With How Severity Is Assessed

A primary challenge of severity-based classification schemes for asthma is that the severity category to which a patient is assigned varies according to the measure used to determine severity. The NAEPP guidelines suggest that evaluation of asthma severity be based primarily on symptoms and objective measures of lung function and, to a lesser extent, assessment of the functional impact of asthma (i.e., the degree to which asthma affects patients’ normal activities). Whereas the guidelines describe specific symptom and lung function criteria corresponding to the various severity levels of asthma, criteria for activity limitation are not defined and are therefore subject to interpretation. The degree of reliance upon particular clinical indices (i.e., symptoms, objective lung function measures, and activity limitation) and the operationalism of these indices impact the severity category to which patients are assigned.

In a US population-based survey conducted in 1998, 56% of patients with asthma were determined to have persistent disease when short-term symptoms (assessed via patients’ 4-week recall) were used to classify severity, whereas 89% were categorized as having persistent disease when severity was classified according to activity limitation (Figure 1). When severity was classified according to global asthma burden, a composite measure including short-term symptoms, long-term (i.e., over the past year) symptoms, and functional impact, 92% of those with asthma were determined to have persistent disease;

### Table 1. NAEPP Classification of Asthma Severity

<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 PEF, ≥80% of predicted PEF variability, &lt;20%</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>Symptoms &gt;2 times/week but &lt;1 time/day</td>
<td>&gt;2 times/month</td>
<td>FEV₁ or PEF, ≥80% of predicted PEF variability, 20% to 30%</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily symptoms</td>
<td>&gt;1 time/week</td>
<td>FEV₁ or PEF, &gt;60% to &lt;80% of predicted PEF variability, &gt;30%</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual symptoms</td>
<td>Frequent</td>
<td>FEV₁ or PEF, ≤60% of predicted PEF variability, &gt;30%</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow. Data from National Asthma Education and Prevention Program.
only 7% were classified as having mild intermittent asthma. The authors concluded that their results emphasize that the distribution of severity is greatly influenced by the type of symptom reports used in a classification system. The NAEPP guidelines do not outline clear-cut points between all levels of symptoms within the severity classification. Therefore, how the NAEPP guidelines are operationalized can influence the distribution of severity reported. The shift in the distribution of symptom burden by inclusion of specific questions on activity limitation illustrates that evaluation of specific day and nighttime symptoms alone may underestimate the impact of asthma on patient's [sic] lives.3

These findings corroborate previous results showing that asthma symptoms considered alone poorly reflect underlying disease severity.4 Asthma symptoms better reflect the current degree of disease control, which does not necessarily correspond to underlying severity of disease (Figure 2).4 Level of control of asthma, which can be measured in terms of lung function or symptoms, can vary markedly over time according to factors such as medication compliance, environmental factors, and the presence of concomitant respiratory illnesses. Thus, while level of control of asthma is partly determined by underlying disease severity, it is modifiable by factors independent of disease severity. Minimal or absent symptoms that reflect good asthma control, for example, can occur in the presence of any degree of underlying disease severity (Figure 2).4

In an attempt to account for the imperfect relationship between asthma severity and control, the NAEPP guidelines specify that symptom and lung function criteria for assigning asthma severity should apply to levels of functioning before pharmacotherapy is commenced.1 The influence of pharmacotherapy—one major determinant of the imperfect relationship between severity and control—is thereby removed.

That symptom measures alone do not accurately reflect asthma severity is not surprising. Asthma is a heterogeneous disease, the severity of which is multiply determined by factors including inflammatory processes and structural changes in
the airways; hereditary influences; environmental contributors; and psychological and emotional characteristics of the patient.\textsuperscript{5,6} In keeping with the heterogeneity of asthma, no single measure adequately gauges patients’ clinical status.\textsuperscript{7} Lung function measures, which provide an objective assessment of airflow obstruction, correlate poorly with symptom measures, which reflect patients’ perceptions of their airflow limitation\textsuperscript{8-11}; and neither lung function measures nor symptom measures are strongly or consistently related to measures of health-related quality of life (ie, patients’ perceptions of their physical, social, and emotional functioning and well-being).\textsuperscript{12-14} Each of these measures appears on the basis of data collected to date to provide unique, largely independent information for assessing clinical status. These considerations highlight the importance of using multiple measures in assessing asthma severity and in determining intervention strategies.

**CHALLENGE 2: ASTHMA IS A VARIABLE DISEASE**

That asthma is a variable disease also poses a challenge regarding attempts to determine a patient’s disease-severity level. Within a given patient, asthma severity can vary depending on several factors,\textsuperscript{15} such as:
- The presence of specific environmental triggers, such as pollen or animal dander
- Physical exercise
- Coexisting respiratory infections
- Time of day
- Emotional stress

Because of these and other contributors to asthma variability, the severity category to which a patient is assigned may vary from one occasion to the next. The variable nature of asthma highlights the need to observe patients longitudinally and to encourage patients to use daily diaries to record asthma symptoms and functional impact. Only with longitudinal follow-up can the patient’s disease severity and the functional impact of asthma be adequately assessed.

**CHALLENGE 3: PATIENTS UNDERREPORT ASTHMA SYMPTOMS**

Patients’ underreporting of asthma symptoms constitutes another challenge to managing asthma according to severity-based classification schemes, such as the NAEPP guidelines, that necessarily rely in part upon patients’ self-reports of symptoms and asthma impact on daily functioning. The tendency of patients to underreport asthma symptoms is illustrated by results of the Asthma in America Survey, a 2509-respondent, nationally representative survey of Americans with asthma.\textsuperscript{16} Of patients who experienced daily symptoms, daily use of a short-acting bronchodilator, exacerbations affecting activity, and exacerbations at least twice weekly (ie, the NAEPP criteria for moderate persistent asthma), 60% considered their asthma to be well controlled or completely controlled, and 58% considered themselves to have mild or no symptoms (Table 2).\textsuperscript{16} Of patients who experienced continual symptoms, limited physical activity because of asthma, and frequent exacerbations (ie, the NAEPP criteria for severe persistent asthma), 32% considered their asthma to be well controlled or completely controlled, and 37% considered themselves to have no or mild symptoms (Table 2).\textsuperscript{16}

**CHALLENGE 4: PATIENTS WITH MILD ASTHMA AND/OR NORMAL SPIROMETRY REQUIRE CAREFUL TAILORING OF THERAPY**

The NAEPP guidelines recommend that pharmacotherapeutic intervention be tailored to asthma severity.

### Table 2. Asthma Severity in Survey Respondents: NIH Severity Index vs Self-Classification

<table>
<thead>
<tr>
<th>Self-Classification of Symptom Severity</th>
<th>Total (%)</th>
<th>Severe Persistent (%)</th>
<th>Moderate Persistent (%)</th>
<th>Mild Persistent (%)</th>
<th>Mild Intermittent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N one</td>
<td>25.1</td>
<td>4.8</td>
<td>10.4</td>
<td>13.1</td>
<td>48.6</td>
</tr>
<tr>
<td>Mild</td>
<td>45.2</td>
<td>31.9</td>
<td>47.2</td>
<td>60.1</td>
<td>42.3</td>
</tr>
<tr>
<td>Moderate</td>
<td>22.9</td>
<td>41.3</td>
<td>36.3</td>
<td>22.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Severe</td>
<td>6.6</td>
<td>21.9</td>
<td>5.8</td>
<td>4.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Not sure</td>
<td>0.2</td>
<td>0</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

NIH = National Institutes of Health.
Data from the Asthma in America Survey.\textsuperscript{16}
ity. Generally, the intensity of pharmacologic intervention is directly related to the level of severity with no pharmacologic intervention recommended for patients in the lowest severity category of mild intermittent asthma. In the NAEPP guidelines, preferred medications by severity category are as follows:

- Low-dose inhaled corticosteroids for mild persistent asthma
- Medium-dose inhaled corticosteroids or low-dose inhaled corticosteroids and long-acting inhaled beta-2 agonists for moderate persistent asthma
- High-dose inhaled corticosteroids combined with long-acting inhaled beta-2 agonists for severe persistent asthma
- No daily medication for mild intermittent asthma

This framework for prescribing is helpful as a starting point for treatment decisions but, rigidly interpreted, can be misapplied—particularly in the management of patients with mild asthma. Both physiologic considerations and clinical data suggest that, contrary to a strict reading of the NAEPP guidelines, pharmacotherapy may be important for patients with mild asthma—even those with mild intermittent asthma or normal spirometry:

- First, the pathological airway inflammation underlying asthma is present even in patients with mild disease and normal lung function, and pharmacologic therapy can mitigate these inflammatory signs.
- Second, even patients with mild asthma are at risk for severe exacerbations and even death from asthma, and pharmacologic therapy is necessary to help these patients.
- Finally, clinical studies demonstrate that even patients with normal spirometry and mild asthma can benefit significantly from daily controller therapy.

**AIRWAY INFLAMMATION IS PRESENT EVEN IN PATIENTS WITH MILD DISEASE**

Asthma is caused by chronic airway inflammation mediated by immune cells, such as mast cells, eosinophils, T-lymphocytes, and neutrophils. These immune cells and respiratory epithelial cells release cytotoxic and inflammatory mediators to cause the edema, excessive mucus secretion, impairment of mucociliary clearance, and increased reactivity of respiratory smooth muscle characterizing asthma. These pathophysiologic changes lead to obstruction of airflow and airway hyperresponsiveness, the 2 primary clinical characteristics of asthma, and contribute to airway remodeling—that is, permanent changes in the structure of the airway mucosa and smooth muscle that possibly culminate in irreversible lung disease.

Some level of airway inflammation is chronically present even in patients with mild asthma. For example, in a study of newly diagnosed adults with asthma and near-normal lung function, characteristic markers of inflammation, including disrupted ciliated epithelium, eosinophilic infiltration, and subbasement membrane collagen deposition, were apparent in bronchial biopsy specimens. Others have observed similar inflammatory changes in patients with near-normal lung function.

Inhaled corticosteroids constitute the foundation of pharmacotherapy for asthma because of their broad range of anti-inflammatory effects. Some evidence suggests that delay in initiation of inhaled corticosteroids may be detrimental for long-term outcomes in asthma. In 2 studies of patients with asthma, the magnitude of improvement in pulmonary function after initiation of an inhaled corticosteroid was inversely related to the time between onset of asthma and initiation of pharmacotherapy with the corticosteroid. It is hypothesized that the longer airway inflammation goes unchecked, the more likely airway remodeling is to occur and the less likely patients are to respond to pharmacotherapy. Good control of asthma early in its course, while it is mild, may prevent or retard the development of more serious asthma and the irreversible airway remodeling associated with chronic inflammation.

**EVEN PATIENTS WITH MILD ASTHMA ARE AT RISK FOR SEVERE EXACERBATIONS AND DEATH FROM ASTHMA**

The NAEPP guidelines emphasize that patients at any level of asthma severity can experience mild, moderate, or severe exacerbations—a fact that can be overlooked in managing a patient with mild asthma with apparently normal lung function. In a study of nearly 14,000 children followed up over a 15-year period, 27% of patients with an FEV₁ of 100% to 120% of predicted value experienced at least 1 exacerbation over 1 year. In another study conducted in Victoria, Australia, 33% of asthma-attributed deaths among children or adolescents over a 3-year period occurred in those who had been classified as having mild or no asthma. The majority of the deaths that were judged...
to have been preventable were attributed to inadequate assessment of or pharmacotherapy for asthma.

**Patients With Normal Spirometry and Mild Asthma Can Benefit From Daily Controller Therapy**

Recent data showing that patients with normal spirometry and mild asthma can benefit from daily controller therapy have called into question the practice of withholding daily pharmacotherapy from patients with mild intermittent asthma, although more research needs to be conducted before definitive conclusions can be drawn. In a randomized, double-blind, crossover study, adults with mild asthma requiring only occasional acute bronchodilator therapy were given the inhaled corticosteroid budesonide (800 µg twice daily) or placebo for 4 weeks and, after a 4-week washout period, were crossed over to the other treatment. The results show that the inhaled corticosteroid significantly improved both lung function and inflammatory markers (Figure 3). Percentage of predicted FEV₁, morning and evening PEF, mean PEF variability, exhaled nitric oxide, and sputum eosinophil counts were all significantly improved by budesonide compared with placebo.

Similar results have been obtained in other studies of patients, including young children, with mild asthma. In the Childhood Asthma Management Program (CAMP), 1041 patients (age, 5 to 12 years) with a pre-beta-agonist FEV₁ value of 94% of predicted were followed up for 4 to 6 years. Patients taking budesonide had a 40% to 45% reduction in prednisone bursts as well as decreased emergent care visits and hospitalizations compared with patients taking placebo.

Thus, a considerable body of evidence shows that patients with mild asthma can benefit from daily controller pharmacotherapy, and some data suggest delaying the initiation of daily controller therapy until asthma has become moderate or severe may lead to a poor therapeutic response compared with response when therapy is initiated early, when asthma is mild. These data require confirmation, and their implications need to be more fully considered before daily controller therapy can be recommended for all patients, including those with mild intermittent asthma. At a minimum, however, these findings highlight the importance of careful monitoring and tailoring of therapy for the patient with mild asthma. Although not all patients with mild asthma require daily controller therapy, many can benefit from it. Each patient should be managed individually, and therapeutic choices should be guided, but not dictated, by the NAEPP guidelines.

**Implications for Patient Care**

Accurate assessment of asthma severity is crucial in ensuring the patient's health and well-being. The consequences of misappraisal of patients' clinical status include unnecessary prescription of medication when
severity is overestimated and failure to intervene with resulting deterioration of asthma control—possibly culminating in death—when severity is underestimated. This review reveals that applying the NAEPs severity-based classification of patients with asthma in clinical practice can be challenging, particularly in the care of patients at the mild end of the asthma severity continuum. The variable nature of asthma, the poor concordance among measures of asthma severity, and patients tendency to underreport their asthma symptoms can contribute to inaccurate severity assessments, which can lead to inappropriate therapeutic choices, such as undertreatment. Undertreatment of the patient with mild asthma can be as dangerous as undertreatment of patients with more severe disease. By keeping the challenges associated with severity-based stratification of patients top-of-mind, healthcare providers may be better able to overcome them in clinical practice.

REFERENCES


