Classifying Asthma*

LeRoy M. Graham, MD, FCCP

The most widely known method of asthma classification is the severity classification recommended in the National Asthma Education and Prevention Program 1997 guidelines, which also formed the basis of the Global Initiative for Asthma guidelines. This method was developed to direct a hierarchy of asthma therapy based on the patient's severity of disease. However, this severity classification has not been validated and has a number of limitations; in particular, it is challenging for physicians to apply reliably. Moreover, it does not allow asthma control to be assessed after the initiation of treatment, even though symptom control is a key objective of the treatment guidelines. A number of tools have been evaluated to provide longitudinal information on asthma control, and some of these have been validated. Clinically relevant measures of inflammation, such as eosinophilic airway inflammation, may also be helpful in classifying asthma and in guiding the use of antiinflammatory therapy. This may be a particularly useful approach in patients who are asymptomatic but have poor lung function, by permitting physicians to determine whether inflammatory processes are active, thus requiring ICS therapy. In the clinical setting, easy-to-use tools are needed to enable longitudinal assessments of symptom control and (ideally) disease progression. ***(CHEST 2006; 130:13S–20S)***

Key words: asthma; asthma classification; asthma control; asthma guidelines; asthma severity

Abbreviations: GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; NAEPP = National Asthma Education and Prevention Program; PEF = peak expiratory flow

The reasons for classifying asthma are wide ranging. From a research perspective, classification is needed to select appropriate and comparable patient populations for inclusion in clinical trials, and to facilitate understanding and evaluation of health outcomes after intervention. From a social perspective, the cost and burden of illness need to be investigated; from a clinical perspective, appropriate pharmacotherapy needs to be determined. Ideally, asthma classification should also provide a guide to treatment with the potential to alter the natural history of the disease. Based on these varied requirements, we know that there is utility for classifying asthma. However, it is important that any clinical tool for classifying asthma is both reliable and valid and can be applied easily to a range of clinical situations and patient groups.

Classifying asthma into different patient groups with different needs for management has been a key component of guideline development. The National Asthma Education and Prevention Program (NAEPP) 1997 guidelines adopted a "stepped-care"

*From the Morehouse School of Medicine, Georgia Pediatric Pulmonology Associates, Atlanta, GA.

Dr. Graham is a member of advisory boards for Merck and GlaxoSmithKline, and is a member of the speakers bureaus of AstraZeneca, Merck, and Sepracor.

Manuscript received July 2, 2005; revision accepted March 20, 2006.

Correspondence to: LeRoy M. Graham, MD, FCCP, Morehouse School of Medicine, Georgia Pediatric Pulmonology Associates, PC, Suite 450, 1100 Lake Hearn Dr, Atlanta, GA 30342; e-mail: LMG254@aol.com

DOI: 10.1378/chest.130.1_suppl.13S

approach to pharmacotherapy: increasing treatment intensity with asthma severity.[1] This approach also forms the basis of the Global Initiative for Asthma (GINA) guidelines.[2] To apply the stepped-care approach, clear determinants are required for where the patient "steps" for initial therapy and the criteria for stepping-up or stepping-down therapy. The expert panel recommended using a severity classification, determined by symptoms and pulmonary function, which was used to direct pharmacotherapy (Table 1).[1] Despite widespread awareness of the NAEPP 1997 guidelines, severity classification still provides many challenges to practicing physicians, which may manifest as a poor adherence to or poor understanding of treatment guidelines. Baker et al[3] showed that a low level of agreement among a group of pediatric asthma specialists in classifying asthma severity led to substantial variability in the treatments recommended. In this article,[3] 14 board-certified pediatric allergists and pulmonologists classified eight case studies; the overall agreement in asthma classification between these specialists was poor (κ statistic = 0.29, where < 0.4 is poor agreement, 0.4 to 0.75 is fair-to-good agreement, and > 0.75 is excellent agreement). The aims of the present article are to examine the difficulties in applying the severity classification in practice, and to discuss alternative approaches to classifying asthma.

Asthma Classification and Diagnosis

In order for any asthma classification to be useful, it is assumed that physicians can accurately and reliably diagnose asthma as a distinct clinical entity. Unfortunately, this may not always be the case (the subject of underdiagnosis is also discussed in this supplement in the article by Humbert). A survey of 571 Massachusetts pediatricians found considerable heterogeneity in the factors they considered most important for diagnosing asthma in young children.[4] The majority (91.4%) of clinicians in this study were familiar with the NAEPP 1997 guidelines, 62.3% had attended a lecture on pediatric asthma in the last 6 months, and 72.7% taught residents/medical students. Despite this level of education, age of the child (> 2 years), and absence of fever during suspected asthma episode were cited by 23% and 18% of respondents, respectively, as being factors important to diagnosis. Neither of these factors are included in the NAEPP 1997 guidelines.[1] In addition, 37% of clinicians in this survey did not find measures of pulmonary function necessary for asthma diagnosis.[3] This may reflect the difficulty in obtaining peak expiratory flow (PEF) in young children,[5] but it is not consistent with the NAEPP 1997 guidelines.[1] Clearly, clinical diagnosis of asthma is unreliable; however, if the disease cannot be reliably diagnosed, then any form of classification will be flawed. Further educational efforts and studies in the pathophysiology of the disease that may lead to quick and definitive diagnostic tests may mitigate this effect to the point where it becomes minimal, but it is something that needs to be considered at least in the present situation. Readers are directed to the report[2] for a more in-depth discussion on asthma diagnosis including the reliability of objective testing for variable airflow obstruction and airway responsiveness.

Basis for Severity Classification

Many clinical factors could potentially be used to classify asthma severity. The NAEPP 1997 severity classification is based on three equally weighted domains: daytime symptoms, nocturnal symptoms, and pulmonary function.[1] However, there is debate as to whether the clinical domains used actually measure asthma severity for all patients.

FEV_1 vs PEF

The interchangeable use of FEV_1 and PEF in guidelines has been criticized.[4] Comparison of 1,198 paired samples from 25 asthmatic patients attending a hospital-based chest clinic found that using either FEV_1 or PEF often resulted in different severity classifications for the same patient (Fig 1).[6] Overall, concordance in severity classification was demonstrated for the two measures in only 49.9% of paired samples. The authors[6] concluded that guidelines should avoid suggesting parity between FEV_1 and

Table 1—*NAEPP 1997 Guidelines Severity Classification and Recommended Pharmacotherapy*

Severity Classification	Recommended Pharmacotherapy
Mild intermittent	No daily medication; as-needed short-acting β_2-agonist
Mild persistent	As-needed short-acting β_2-agonist; low-dose ICS or other antiinflammatory
Moderate persistent	As-needed short-acting β_2-agonist; medium-dose ICS or low-dose ICS plus long-acting bronchodilator; increase ICS dose and add long-acting bronchodilator if needed
Severe persistent	As-needed short-acting β_2-agonist; high-dose ICS plus long-acting bronchodilator plus oral corticosteroids

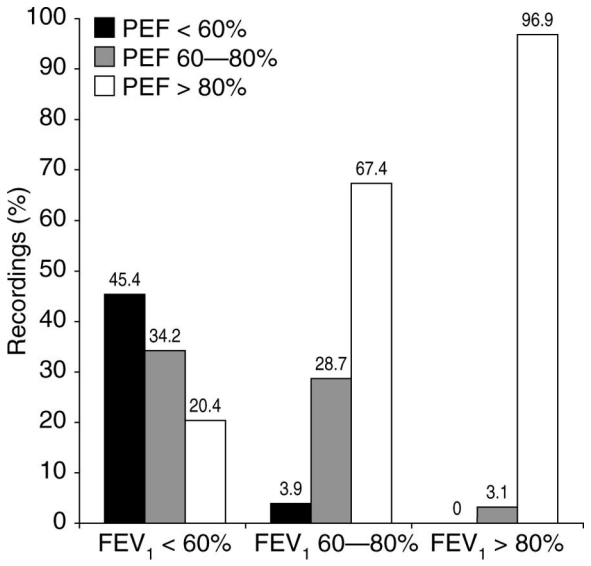

FIGURE 1. Degree of concordance between FEV_1 and PEF paired values from patients with asthma and impact on severity classification (n = 1,198 paired samples in 25 patients). Adapted from Sawyer et al.[6]

PEF measurements. Similar results illustrating a lack of agreement between FEV_1 and PEF were described in a study[7] of 2,587 paired measurements from 101 patients with asthma or COPD. In a study[8] of children with impaired lung function, the frequency of normal PEF measurements was found to increase with asthma severity. These findings give cause for concern, as failure to recognize worsening symptoms in children with severe asthma could lead to serious adverse outcomes.

Variability and Correlation of Severity Measures

A number of studies[9–12] have found a dissociation between asthma severity based on symptoms and measures of lung function. For example, a study[10] in children found that, when asthma severity was based on symptoms or medication use, there was no relationship between the NAEPP 1997 severity classification and FEV_1. A reanalysis[13] of data from two large, randomized controlled clinical trials (n = 1,576) found large within-patient variability and no more than a moderate correlation between the changes in FEV_1 and PEF, FEV_1 and daily symptoms score, and daily symptom score and β_2-agonist use. Considerable intrapatient variability in asthma severity classification over time was also demonstrated in a study[14] of 85 steroid-naïve patients. At baseline, all patients met the criteria for moderate or severe persistent asthma. However, the mean percentage of the 12 treatment weeks when these patients would be reclassified as having intermittent, mild, moderate, and severe asthma was 9%, 14%, 71%, and 6%, respectively. This variability was dependent on changes in any one of the measures of severity: PEF, β_2-agonist use, or symptoms.[14] The lack of correlation between the factors used in the NAEPP 1997 severity classification is of concern, as they can all be used to make the final severity assessment. In addition, the observed variability over time means that a severity classification may depend on which particular day that patient is assessed and their recent symptom history.

Effect of "Worst Variable" Rule

The worse variable rule in the NAEPP 1997 guidelines means that patients should be classified according to the worse severity level that any of the factors used in the severity classification places them. So, if the patient is classified as moderate persistent based on FEV_1 but severe persistent based on nocturnal symptoms, then the patient would be classified as severe persistent.

In a study designed to assess asthma burden in the United States, the severity classification was found to increase as additional factors were taken into account.[15] Trained interviewers surveyed 42,022 households of adult patients and parents of children with current asthma. Based on daytime symptoms, 19.1% of patients had moderate-to-severe disease, vs 28.2% when nocturnal symptoms were used. Combining daytime and nocturnal symptoms greatly increased the prevalence of moderate-to-severe disease (35.9%). Depending on whether short-term or long-term symptoms were used, 39% of patients were classified differently. Overall, the investigators[15] concluded that the assessment of global asthma burden was influenced by the discordance observed in how individual subjects report asthma symptoms. On the basis of the severity criteria derived from the NAEPP 1997 guidelines, only a minority of individuals (7.3%) were classified as having a global asthma burden consistent with mild intermittent disease; the large majority (77.3%) were classified as having moderate-to-severe disease.[15]

Lack of consistency between the three clinical domains in the NAEPP 1997 severity classification was demonstrated in a large study[16] of 744 inhaled corticosteroid (ICS) nonusers and 685 ICS users recruited to the pretreatment phase of five clinical trials. Patients completed daily diary cards, and methods were standardized throughout the study population. Based on the worse variable rule, in the ICS nonuser group nocturnal symptoms determined the final severity classification for the majority of patients, with most classified as severe persistent (55.0% of patients). The classification of such a high

proportion of patients as having persistent severe asthma in this study is a concern, and the authors[16] suggested a cautious approach to the use of severity classification based on the NAEPP 1997 guidelines.

Severity Classification in Practice

A study[17] in a US teaching hospital investigated the performance of different groups of physicians regarding various different aspects of the NAEPP 1997 guidelines. A total of 108 physicians completed the test, scoring only 46 ± 2.3% in their estimation of asthma severity. There were no differences between the primary care faculty, fellows, or asthma specialists in their performance, but residents had significantly worse scores than the other three groups (36 ± 2.4%, $p < 0.05$). Most of the errors in estimating severity led to an underestimation. This study[17] was performed quite soon after the guidelines were published, and suggested that all physicians could benefit from further training regarding severity estimation. However, subsequent reports[15,17,20] call into question whether further education would improve the reliability of severity classification.

In the context of using the NAEPP 1997 classification in everyday practice, a study[18] in an urban teaching hospital evaluated chart records of physician-rated asthma severity vs severity determined using a structured survey administered to parents of children with scheduled visits for asthma. Charts were surveyed for 176 patients, 77% of which had a documented severity classification. Severity classification of the same patient varied significantly between the charts and survey for all levels of classification ($p = 0.001$) [Fig 2]. Physicians underestimated the severity of their patients' asthma, and this led to misclassification. Patients who had been classified correctly were more likely to receive appropriate medication. For example, none of the patients with severe persistent asthma were correctly classified, and only 54% of these patients were receiving ICS. Interestingly, correct chart classification was not related to the level of physician training. Combined with the fact that this was an academic hospital, these findings suggest that the problem with severity classification may not just be a lack of physician education, but may also be due to inherent difficulties in applying the severity classification in practice.

Studies[17–19] of asthma classification by physicians consistently show that asthma severity is underestimated vs the NAEPP 1997 classification. It is unclear whether these findings represent nonadherence by physicians, misinterpretation of the severity classification, or indicate that physicians modify their severity classification to allow for what they perceive to be an inherent overestimation of asthma severity in the guidelines. However, it is clear is that using severity classification is difficult in practice, and this may lead to inappropriate pharmacotherapy.

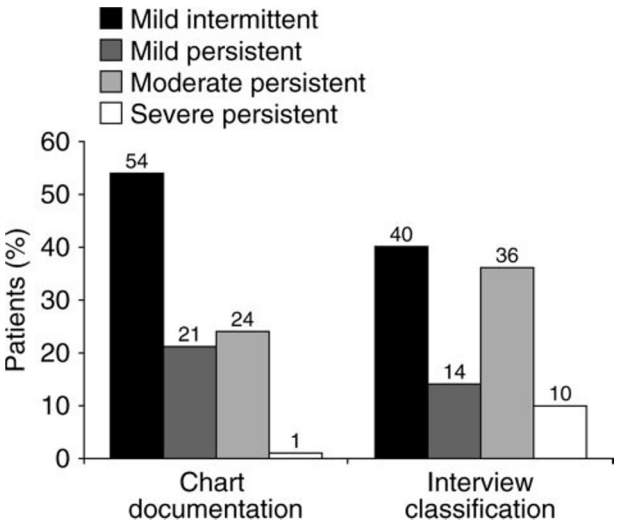

Figure 2. Differences between NAEPP 1997 severity classification recorded on pediatric patients' charts and as determined by structured interview of patients' parents (n = 176; $p = 0.001$ for each comparison of chart vs interview). Adapted from Braganza et al.[18]

Severity vs Control

Severity assessment requires the absence of medication, and this presents a real-life problem. In practice, it is part of routine management to step-down therapy in stable, well-controlled patients to try to maintain control with minimum therapy. If the step-down is well tolerated, this may mean that the patient's severity classification has changed in the intervening years since treatment initiation. It would seem intuitive that disease severity in asthma would be dynamic over time and might well be modified by treatment, patient education and trigger avoidance. However, the current model for assessing disease severity does not allow changes in severity to be measured over time once medication has been started, and thus it cannot be used to assess symptom control or treatment outcome.[14,20]

The relationship between asthma severity, control and treatment can be thought of as follows: asthma severity + (pharmacotherapy + allergen/trigger avoidance) = asthma control; or asthma severity = asthma control – (pharmacotherapy + allergen/trigger avoidance). This relationship is true only if the minimum amount of pharmacotherapy is used to control symptoms. In practice, this would normally

be the amount of ICS or oral corticosteroids required in severe illness. However, once again there is a real-life problem; using ICS use as a surrogate for severity relies on asthma patients being titrated to the correct dose and not being either overtreated or undertreated. The amount of medication required will also depend on the extent of allergen/trigger avoidance, and this may vary seasonally. Thus, in many settings, if asthma classification is based on ICS use then it is measuring a variable mix of asthma control, physician prescribing practices, patient adherence, allergenic burden or exposure to triggers, and access to medicine, with no means of separating the contributing components.

Options for Asthma Classification

It may be too much to ask that one tool should meet all the clinical requirements for asthma classification, particularly given the dissociation between symptoms/lung function and underlying disease severity in terms of the inflammatory process. New measures of asthma severity are likely to be of most value if they can be shown to directly influence disease management; a variety of measures, such as symptom control questionnaires, variable flow obstruction, disease progression, exacerbation frequency, and airway inflammation, among others, are likely to prove most helpful. As it is beyond the scope of this article to explore all of the various options for severity classification and asthma management, only those highlighted in the meeting are described here. For further information, readers are directed to the current literature.[20–24]

Measures of Airway Inflammation

In a randomized study, asthma management based on normalization of induced-sputum eosinophil count, along with symptom reduction, was shown to reduce severe asthma exacerbations and hospital admissions vs management based on British Thoracic Society guidelines.[25] Other markers of airway inflammation, such as exhaled nitric oxide, may allow a relationship between severity and control to be established.[26] These options are not currently practical outside clinical studies but may be adapted in the future for more widespread clinical use. The article on "Treating asthma as an inflammatory disease" has further information on inflammatory markers.

Measures of Symptom Control

Alternatively, classification could be focused on asthma control. Control of symptoms includes both pharmacotherapy and allergen avoidance, an area that is covered separately from pharmacotherapy in the NAEPP 1997 and GINA guidelines.[1,2] Variables such as life-threatening asthma attacks, hospitalizations, and emergency department visits could also be included. Classifying asthma based on symptom control implies a more patient-focused, tailored approach to therapy, which is flexible enough to change over time rather than a set solution for every patient assigned to a particular category at one point in time.

Any measure of symptom control needs to be multidimensional to overcome the effects of patients underestimating their symptoms. This has been shown in surveys in the United States and Europe, with many patients initially reporting that their symptoms are well controlled until further questioning reveals that their symptoms are, in fact, significant.[19,27,28] A number of multidimensional instruments have been developed and validated based on symptom control.[29–32]

The Asthma Control Questionnaire was developed from of a list of symptoms ranked by 100 asthma clinicians who were members of guidelines committees in 18 countries.[29] The top five symptoms plus β_2-agonist use and airway caliber were included in the final seven-point measure. The tool was assessed in a 9-week study in 50 adults with asthma, which showed a high level of interclass reliability and high responsiveness to changes in asthma control. Concurrent validity with other measures of asthma health status was demonstrated in these adult patients.[29]

The Asthma Therapy Assessment Questionnaire was developed for use in population-based disease management.[30] It is based on a simple index of control problems ranging from no control problems to four. When applied to 5,181 adults, there were significant associations between the questionnaire and self-reported health-care utilization and quality of life using generic and disease-specific instruments.[30] Rates of acute care episodes were 3.5 times more likely for patients with three or four control problems, 1.7 times for those with two control problems, and 1.4 times for those with one control problem vs those with no control problems; all of these differences were significant.[33]

The Asthma Control Test is a patient-based tool for identifying subjects with poorly controlled asthma.[31] The test was developed by triangulating a 22-item survey of 471 patients with specialist-assessed asthma control after spirometry. Five items were then selected for evaluation. The five-item scale demonstrated a good level of internal reliability, and showed concurrence with the specialist's rating of asthma control (overall agreement, 71 to 78%).[31] However, the demonstrated validity of this

measure is dependent on the specialist's opinion of asthma control being correct.

An asthma scoring method based on a percentage scale (100% representing full control/normal) was developed in French-speaking Canada based on symptoms, lung function and, optionally, airway inflammation assessed using sputum eosinophil concentration.[32] Most patients in this study[32] had relatively well-controlled asthma, and concordance was noted between symptom control and the Mini-Asthma Quality of Life Questionnaire. The reliability and validity of this tool need further investigation in different patient groups and in an English-language form.

Participant Feedback and Discussion

Workshop participants were asked to address the following questions related to this presentation:

- What criteria do you use to classify patients?
- How do you use the guidelines in recommending treatment?
- If you adhere to asthma guidelines in your practice, which do you use? If not, why not?
- What specific limitations are there to the current severity classifications?
- What are the clinical consequences and limitations of the use/nonuse of a treatment algorithm in your practice?
- Regarding classification, what could be done to make it easier for physicians to classify patients?

There was considerable variation among the participants in this meeting regarding the methods used to classify asthma. The GINA and NAEPP 1997 guidelines were thought to be a useful reference source, but the severity classification was found to be somewhat conflicting and impractical to apply in a day-to-day clinical setting. In all, 64% of participants believed that the GINA severity classification needed to be either amended or eliminated. There was thought to be considerable underuse of the guidelines in terms of severity classification. Only 21% of participants used the GINA classification at least 60 to 90% of the time, with 30% using it < 20% of the time or never. The participants believed that these results would be similar in the primary care setting.

Reliability of the GINA severity classification was also informally tested with the participants in this American College of Chest Physicians meeting, applying criteria similar to those used in the study by Baker et al.[3] Using four case studies, 25 asthma specialists were asked to provide a severity classification for each patient, identify the most important factors that they used to reach this classification, and suggest additional diagnoses and recommended treatments. Figure 3, *top*, shows that the experts disagreed with the severity classification based on the GINA guidelines in 30% of cases. In addition, there was variability between experts, particularly regarding the mild persistent and moderate persistent cases. This variation appeared to be dependent on the factors that each expert considered important for determining severity; these were mainly consistent for the mild intermittent and severe persistent cases, but varied considerably for the mild persistent and moderate persistent cases. The mild persistent and moderate persistent cases also had the greatest variation in treatment recommendations (Fig 3, *bottom*). All of the physicians who took part in this exercise were wholly familiar with the guidelines and severity classification.

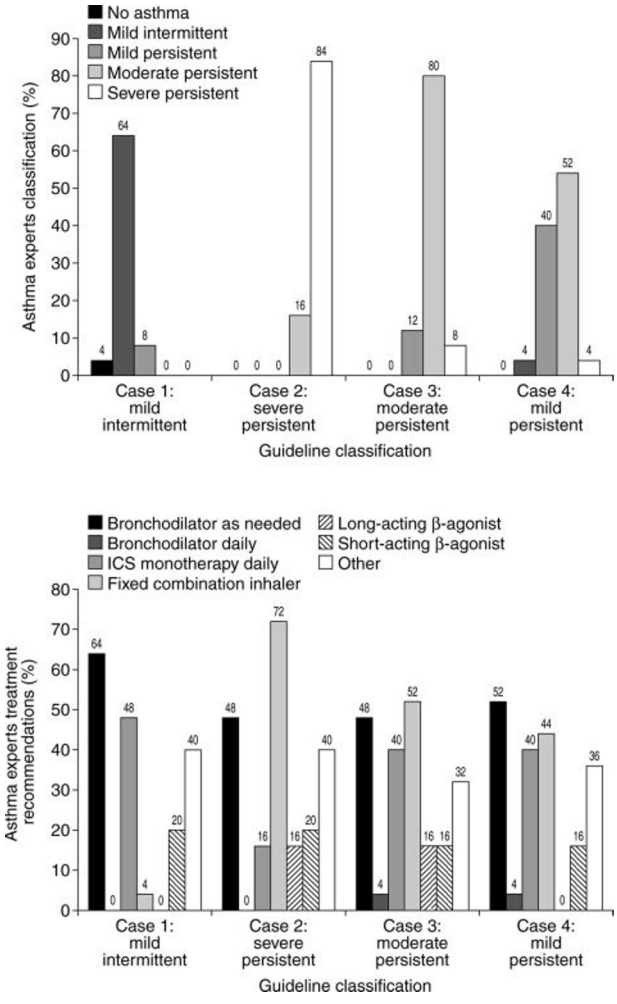

Figure 3. Responses of 25 asthma experts participating in the meeting on four case studies for severity classification compared with classification based on GINA guidelines (*top*), and treatment recommendations (more than one response permitted per participant) [*bottom*].

There was concern over the poor evidence base to support current models of asthma severity classification. For example, there is a lack of evidence in determining the cutoffs between intermittent and persistent and mild, moderate, and severe. These cutoffs are critical as they are used to determine therapy, but they have not been validated except in the case of hospitalizations and mortality, outcomes that affect only the minority of asthma patients. In addition, the cutoffs for lung function are absolute, based on percentage predicted of normal, and do not recognize changes in lung function for an individual patient, for example, percentage of predicted FEV_1 from 120 to 80%.

From a clinical perspective, the desired outcome is clearly asthma control, and this is what our clinical decisions should be based on. Bronchodilator response and lung function should still be determined to define the diagnosis and disease state, as well as to assess therapeutic effect.

Conclusions

There is no doubt that asthma classification is a complex area with many unknowns. The NAEPP 1997 guidelines represented an excellent start in defining the hierarchy of medications based on asthma severity, and these same principles were carried into GINA. However, the application of the severity classification in practice is fraught with difficulty and uncertainty. Are patients with asthma being classified correctly on a day-to-day basis? Probably not. Does the severity classification accurately reflect disease status? Probably not. Does misclassification of patients result in inappropriate pharmacotherapy? Yes.

From a clinical perspective, the separation between disease severity and symptom control needs to be maintained, while appreciating the different risk profiles of patients for adverse outcomes and adverse effects of therapy. It is also important to recognize that uncontrolled symptoms and adverse outcomes may be due to exacerbation of disease, undertreatment, poor compliance, or inadequate health care. Additional medication will certainly be required during exacerbations. However, flexibility in the pharmacotherapy prescribed and an agreed-on management plan are needed to allow appropriate step-up and step-down of therapy within the context of an effective physician/patient relationship.

The challenge is to develop a tool for asthma classification that is easy to use, applicable in a variety of clinical settings, and that effectively guides therapy that improves daily functioning and outcomes for patients with asthma. Since asthma is a multidimensional disease, we can develop classification of different aspects of the disease that in turn may require different management approaches.

ACKNOWLEDGMENT: The author thanks Naomi Richardson, MSc, for writing and editorial support in the development of this article.

References

1 National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health, 1997; publication No. 97–4051
2 Global Initiative for Asthma. GINA workshop report, global strategy for asthma management and prevention. Available at: www.ginasthma.com/wr_clean.pdf. Accessed October 22, 2004
3 Baker KM, Brand DA, Hen J Jr. Classifying asthma: disagreement among specialists. Chest 2003; 124:2156–2163
4 Werk LN, Steinbach S, Adams WG, et al. Beliefs about diagnosing asthma in young children. Pediatrics 2000; 105: 585–590
5 Gorelick MH, Stevens MW, Schultz T, et al. Difficulty in obtaining peak expiratory flow measurements in children with acute asthma. Pediatr Emerg Care 2004; 20:22–26
6 Sawyer G, Miles J, Lewis S, et al. Classification of asthma severity: should the international guidelines be changed? Clin Exp Allergy 1998; 28:1565–1570
7 Llewellin P, Sawyer G, Lewis S, et al. The relationship between FEV_1 and PEF in the assessment of the severity of airways obstruction. Respirology 2002; 7:333–337
8 Eid N, Yandell B, Howell L, et al. Can peak expiratory flow predict airflow obstruction in children with asthma? Pediatrics 2000; 105:354–358
9 Palma-Carlos AG, Palma-Carlos ML. Correlation between clinical classification, PEF and FEV_1: guidelines and reality. Allerg Immunol (Paris) 2003; 35:130–132
10 Bacharier LB, Strunk RC, Mauger D, et al. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004; 170:426–432
11 Mitra AD, Ogston S, Crighton A, et al. Lung function and asthma symptoms in children: relationships and response to treatment. Acta Paediatr 2002; 91:789–792
12 Sharek PJ, Mayer ML, Loewy L, et al. Agreement among measures of asthma status: a prospective study of low-income children with moderate to severe asthma. Pediatrics 2002; 110:797–804
13 Zhang J, Yu C, Holgate ST, et al. Variability and lack of predictive ability of asthma end-points in clinical trials. Eur Respir J 2002; 20:1102–1109
14 Calhoun WJ, Sutton LB, Emmett A, et al. Asthma variability in patients previously treated with β_2-agonists alone. J Allergy Clin Immunol 2003; 112:1088–1094
15 Fuhlbrigge AL, Adams RJ, Guilbert TW, et al. The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines. Am J Respir Crit Care Med 2002; 166:1044–1049
16 Colice GL, Burgt JV, Song J, et al. Categorizing asthma severity. Am J Respir Crit Care Med 1999; 160:1962–1967
17 Doerschug KC, Peterson MW, Dayton CS, et al. Asthma guidelines: an assessment of physician understanding and practice. Am J Respir Crit Care Med 1999; 159:1735–1741
18 Braganza S, Sharif I, Ozuah PO. Documenting asthma sever-

ity: do we get it right? J Asthma 2003; 40:661–665
19 Asthma in America: a landmark survey. GlaxoSmithKline, 1998. Available at: http://www.asthmainamerica.com. Accessed May 15, 2006
20 Fuhlbrigge AL. Asthma severity and asthma control: symptoms, pulmonary function, and inflammatory markers. Curr Opin Pulm Med 2004; 10:1–6
21 Haahtela T. Assessing airway inflammation: from guessing to quantitative measurements. Ann Med 2002; 34:74–76
22 Colice GL. Categorizing asthma severity and monitoring control of chronic asthma. Curr Opin Pulm Med 2002; 8:4–8
23 Wark PA, Gibson PG. Clinical usefulness of inflammatory markers in asthma. Am J Respir Med 2003; 2:11–19
24 Vollmer WM. Assessment of asthma control and severity. Ann Allergy Asthma Immunol 2004; 93:409–413
25 Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002; 360:1715–1721
26 Delgado-Corcoran C, Kissoon N, Murphy SP, et al. Exhaled nitric oxide reflects asthma severity and asthma control. Pediatr Crit Care Med 2004; 5:48–52
27 Vermeire PA, Rabe KF, Soriano JB, et al. Asthma control and differences in management practices across seven European countries. Respir Med 2002; 96:142–149
28 Kuehni CE, Frey U. Age-related differences in perceived asthma control in childhood: guidelines and reality. Eur Respir J 2002; 20:880–889
29 Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14:902–907
30 Vollmer WM, Markson LE, O'Connor E, et al. Association of asthma control with health care utilization and quality of life. Am J Respir Crit Care Med 1999; 160:1647–1652
31 Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004; 113:59–65
32 Boulet LP, Boulet V, Milot J. How should we quantify asthma control? A proposal. Chest 2002; 122:2217–2223
33 Vollmer WM, Markson LE, O'Connor E, et al. Association of asthma control with health care utilization: a prospective evaluation. Am J Respir Crit Care Med 2002; 165:195–199