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REVIEW ARTICLE

What Are the Determinates of Asthma Control?

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The evolution of our understanding of treatment of asthma begins with assessment of severity which is primarily related to the natural history of the disease. Control is defined as normalizing of the physiologic abnormalities and lessening economic and social burden of the disease. This paper reviews the factors that influence the variability and determinants of asthma control. The tools to validate and access asthma control should be employed in daily clinical practice.

Therefore, it is important to determine asthma control based on a multidimensional approach including physiologic assessment, global assessment of functionality, daytime symptoms, nighttime symptoms, healthcare utilization, and adherence to therapy.

Keywords asthma control, asthma severity, asthma guidelines, spirometry, measures of inflammation

INTRODUCTION

The current status of asthma control has been set by both national and international guidelines. The 1991 National Heart, Lung and Blood Institute Guidelines for the diagnosis and management of asthma introduced the concept of classification of asthma severity that was to be determined before any pharmacologic therapy was instituted (1). A stepwise approach of escalating pharmacologic therapy was based on asthma severity defined by symptoms and objective measurements of airflow limitation before the institution of therapy. With this approach, the goal was to achieve optimal asthma control using medications or combinations of medications to match the individual's level of asthma severity. The Global Initiative for Asthma (GINA) has set forth a set of goals for asthma treatment as outlined in Table 1 (2).

ASTHMA CONTROL VS. ASTHMA SEVERITY

Any discussion of control will invariably include a discussion of asthma severity with these terms often used interchangeably. It must be stressed that although asthma control and asthma severity are closely related to each other, they measure distinctly different aspects of the disease. Severity is more reflective of the natural history of the disease often determined in childhood and is less likely to vary over the long term, whereas control is reflective of disease activity based on levels of symptoms over a set period. In other words, severity measures the intrinsic components of the disease, while control measures the dynamic aspects of the disease as reflected by day and nighttime symptoms, and need for beta-agonist, which can vary greatly over time. All of us have patients who have severe asthma based on histories of frequent emergency room (ER) visits and hospitalizations as well as need for maximal pharmacotherapy to establish good control. Once well controlled they display few symptoms and may have nearly normal lung function, yet they still have severe disease. This point was well made by Liard et al. (3), who classified severity in 4,362 asthmatics based on symptom scores and FEV_1 values alone and then re-classified patients by need for and dose of inhaled glucocorticoid (ICS) therapy.

Forty percent of all asthmatics initially classified as having mild intermittent asthma (381/953) based on symptoms and lung function alone, were reclassified into other groups (mild, moderate, and severe persistent) when need for and dose of ICS was added to the classification algorithm. In contrast, a patient with mild persistent asthma may have frequent daytime and nocturnal symptoms requiring frequently administered beta-agonists due in large part to inadequate controller medication use. This subject clearly has poorly controlled asthma, but once low-dose ICS therapy is initiated, the patient's asthma control improves significantly with no nocturnal symptoms and rare use of rescue albuterol for symptoms.

A recent study sought to determine the relationship between asthma severity and asthma control by assessing the frequency of ER visits and hospitalizations in a cohort of 1,251 asthmatics over a 12-month study period (4). Asthma control was ascertained by questionnaire in 1,130 subjects with 42% having moderate or poorly controlled asthma based on frequency of symptoms. During the study, 14.8% of the patients reported at least 1 ER visit or hospitalization. In addition, a significant correlation between asthma control based on symptom frequency and need for ER visit or hospitalization was noted ($p < 0.001$). The odds ratio (OR) for a hospital contact in an individual with good control was only 0.5, compared to an OR of 2.2 in patients with poor asthma control. Of importance, this association was seen independent of ICS use and dose of ICS required (the surrogate marker of disease severity), before entry into the study. Patients with poor control were six times more likely to report a hospital contact than patients with good control and three times more likely than patients with moderate control.

ASSESSMENT OF ASTHMA CONTROL INVOLVES MORE AN EVALUATION OF SYMPTOMS AND LUNG FUNCTION IMPAIRMENT

A major limitation of the current guidelines is that they do not take into account other aspects of the disease such as the

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TABLE 1.—Global initiative for asthma (GINA) goals of treatment.

The aim of asthma management should be control of the disease
• Minimal (ideally no) chronic symptoms, including nocturnal symptoms
• Minimal (infrequent) episodes
• No emergency visits
• Minimal rescue SABA (short-acting B_2-agonist) use
• No limitations on activities, including exercise
• Peak expiratory flow variability <20%
• (Near) normal peak expiratory flow
• Minimal (or no) adverse effects from medicine

impact of asthma on quality of life measures. The Asthma in America Survey initially performed in 1998 and updated in 2004 help us better understand the burden of asthma as it relates to asthma control (5, 6). In the first, 42,022 households participated in the screening interview with 91% of households contacted via a cross-sectional, random, and digital dial telephone survey; 3,278 households had one or more people with asthma (7.8% of the households). The analysis included 1,788 adults (>16 years old) and 721 children. The data revealed that 30% of patients had sleep disruption greater than once per week, 32% missed school or work in the past year, 48% had limited sports or recreational activities and 23% had unscheduled emergency room visits in the last year (Figure 1). In addition, there was a mismatch in the patient's level of asthma control based on symptoms and the patient's perception of their level of control with 61% of patients with moderately controlled asthma and 32% of patients with poor control believing that they had well or completely well controlled asthma (Figure 2) (5). This study illustrates how far from the mark we are in achieving the goals GINA have set for us with respect to optimizing asthma control.

A more recent study limited to just children found similar results (6). This survey evaluated 801 children with asthma 4 to 18 years of age. Over 60% of the respondents reported activity limitation, 54% had missed school in the past year, 67% had symptoms in the 4 weeks before the survey, and 54% had at least one sudden severe episode in the last year (Figure 3). In a study by Fuhlbrigge et al. (7), patients with moderate to severe asthma had higher incidence of need for hospitalization, urgent care visits, and missed work or school more than 7 days. In addition, 25% of the patients with mild intermittent asthma had a significant asthma exacerbation during the observation period.

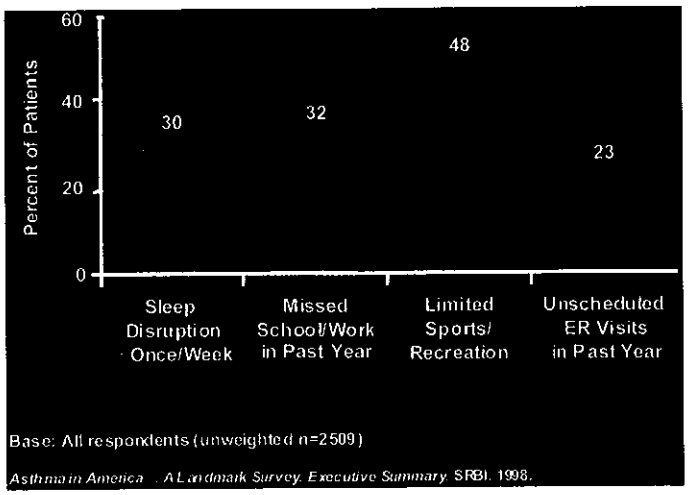

FIGURE 1.—Many patients fail to meet the goals of asthma therapy.

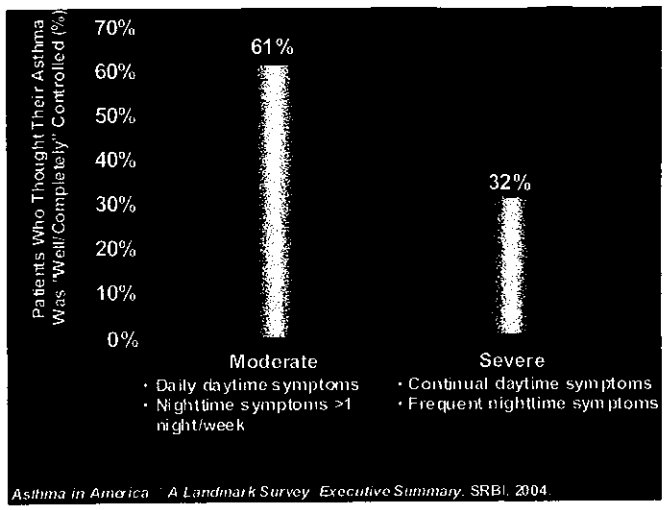

FIGURE 2.—Many patients with frequent sympotoms consider their asthma "well/completely" controlled.

FACTORS THAT INFLUENCE LEVEL OF CONTROL

Factors that influence asthma control is numerous and can be categorized as physiologic, environmental, and behavioral (Table 2) (8). Physiologic factors include the diurnal variability that characterizes asthma. Multiple studies have demonstrated lower lung function, higher levels of inflammatory mediators, and higher levels of airway hyperreactivity among asthmatics in the early morning hours. Another physiologic factor is gender. A greater percentage of asthmatics in childhood will be male, while the inverse is true for adults where there is a female predominance. The association of premenstrual asthma with significant increase in exacerbations and decrease in lung function occurs in approximately one third of female asthmatics. During pregnancy approximately one third of asthmatics worsen; one third remains unchanged, and one third improves. The compounding effect of obesity on asthma is still yet to be defined. There appears to be increasing data suggesting that increased body mass index is associated

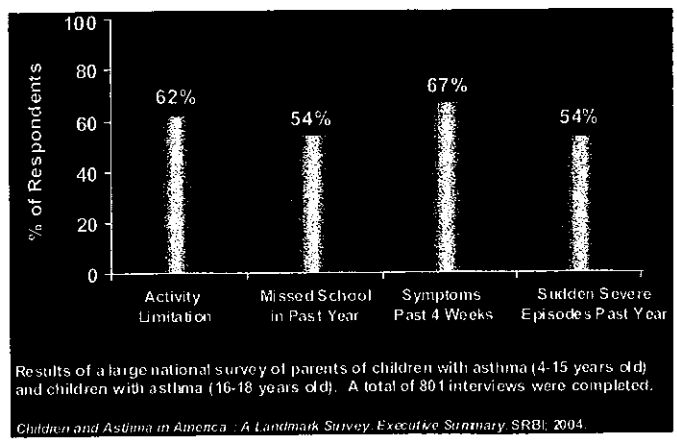

FIGURE 3.—Pediatric asthma in America: goals of asthma therapy are inadequately met.

TABLE 2.—Sources of variability in asthma.[8]

Physiologic
Circadian fluctuations
Hormonal status
Pregnancy
Obesity
Airway remodeling
Airway hyperresponsiveness
Concomitant diseases (e.g., allergic rhinitis, gastroesophageal reflux) refractory asthma
Environmental
Viral infections
Allergens
Seasonal variations
Air pollution
Tobacco
Behavioral
Patient understanding of asthma
Adherence to asthma therapy regiment
Knowledge/avoidance of asthma triggers
Recognition of worsening symptoms

with increasing severity of asthma and possibly medication needs especially in females. The structural changes in the airway and degree of bronchial hyper-responsiveness are not clearly linked but appear to be loosely related to increasing severity of asthma and medication needs. The most common concurrent comorbidities are allergic rhinitis and/or sinusitis and gastroesophageal reflux. Both of which are known to be associated with poor asthma control until these comorbidities are appropriately addressed.

Environmental factors, especially early viral infection with respiratory syncytial virus, may in fact lead to increasing asthma severity in the short term but is associated with protection after puberty for persistent asthma as long as an Immunoglobulin E(IgE)-mediated diathesis has not developed. The two highest statistically linked allergens leading to persistence of asthma symptoms or relapse include alternaria and house dust mite. Air pollution, especially particulate matter and ozone sulfuric oxide, have been associated with decreased lung function and increase in exercise-induced bronchospasm in several large epidemiologic studies. In addition, primary smoking and environmental tobacco smoke are extremely important factors for the development and persistent of bronchial hyper-reactivity, even exposure in utero. Behavioral sources of variability relate to adherence to medication regimen, perception of asthma severity, and appropriate response to escalating symptoms.

Asthmatics Can Display Wide Swings in Control Over Time

Childhood asthma and adult asthma are both significant variable conditions. A recent study by Calhoun et al. in adults analyzed 56 patients with moderate to severe persistent asthma who received placebo during 12-week pharmaceutical sponsored asthma trials found these individuals to display significant variability over the course of the trial with both spontaneous improvement and worsening of symptoms (9). Children who received placebo in similarly designed studies revealed even greater variability. In this study, 276 children 4 to 11 years of age who met the NAEPP criteria for moderate severe asthma received short-acting beta-agonist alone over a 12-week period (10). At entry, all subjects had moderate persistent asthma based on FEV_1, yet during the study, 55% of the weeks were spent in the moderate to severe category. In addition, a number of subjects had wide swings in peak expiratory flow rate (PEF) values during the study with 44% having greater than 10 changes and ~35% of subjects exhibiting $\geq$ 15 changes in asthma severity classification based on PEF during the 12-week period. This highlights again the extreme variability of asthma and need for ongoing assessment and characterization of asthma.

Parameters of Asthma Control

The parameters that have been proposed to determine control are numerous (Figure 4). Physiologic parameters include measurement of peak flow and FEV_1 both at baseline and going forward. FEV_1 is an important marker, but most children with even moderate persistent asthma will have values within the normal range. This was highlighted both in the Childhood Asthma Management Program (CAMP) Study (11), where the mean pre-bronchodilator FEV_1 was 94% of predicted. Similar values were noted among the children enrolled in the START (Inhaled Steroid Treatment As Regular Therapy in Early Asthma) Study (12). Assessment of airway inflammation would ideally be an important measure of control as inflammation is thought to be the cause of poor control.

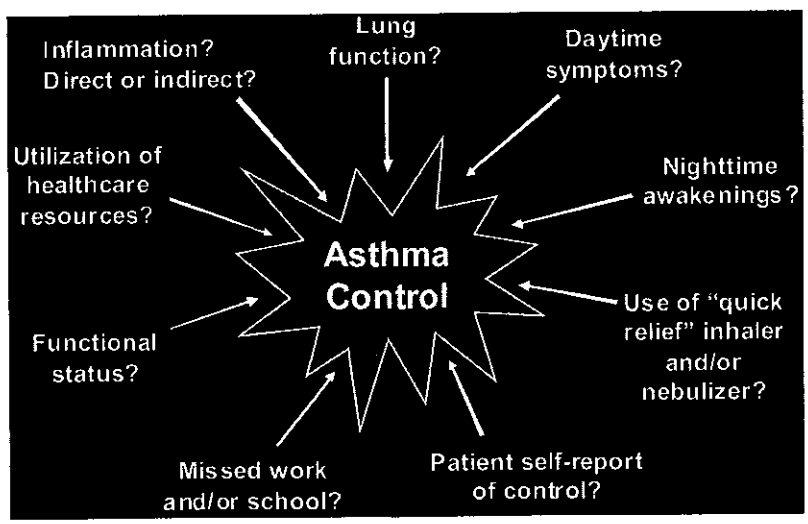

FIGURE 4.—How can asthma control be measured?

TABLE 3.—GOAL definition of control.

Each week*	Total Control All of:	Well Controlled Two or more of:
Daytime symptoms	None	<2 days with score >1
Rescue B_2 –agonist use	None	<2 days & <4 occasions
Morning PEF	>80% predicted every day	>80% predicted every day
Nighttime awakening	None	None
Exacerbations	None	None
Emergency visits	None	None
Treatment-related AEs	None enforcing change in asthma therapy	None enforcing change in asthma therapy

*Maintained for at least 7 out of 8 weeks. AEs = adverse events.

TABLE 4.—Comparison of the asthma control questionnaires.

	ATAQ	ACQ	ACT
Limits daily activity	Yes	Yes	Yes
Shortness of breath	No	Yes	Yes
Disrupts sleep	Yes	Yes	Yes
Albuterol use	Yes	Yes	Yes
Effect on global control	Yes	No	Yes
Frequency of wheeze	No	Yes	No

*Modified from Nathan, RA. Measuring Asthma Control in Clinical Practice. Respiratory Digest 2005; 7:1–11. ATAQ = Asthma Therapy Assessment Questionnaire; ACD = Asthma Control Questionnaire; ACT = Asthma Control Test.

Until recently, there were no readily available non-invasive measures. We now have the ability to measure exhaled nitric oxide (eNO), sputum eosinophils, and breath condensates. Of the non-invasive measures, eNO has the greatest potential to be used in the clinical setting given its ease of use. Its major drawback comes from the cost of the equipment. Several studies have demonstrated associations between asthma control and severity and eNO level with higher levels associated with poor asthma control (13). In addition, asthma control can be improved when eNO levels are normalized (14). As is the case with all parameters, none of these markers of inflammation in isolation gives a comprehensive assessment of a patient's level of asthma control.

Symptoms have long been used to assess control with all the current guidelines relying heavily on both day and nighttime symptoms. Assessment should always include the frequency and severity of daytime and nighttime symptoms and need for quick relief bronchodilator. Other important parameters include the patient's functional/exercise status, the degree of health care utilization, and missed work or school and the patient's own self-reported control.

CAN OPTIMAL ASTHMA CONTROL BE ACHIEVED?

Ideally, as many parameters of control as possible should be collected and followed on an ongoing basis. This concept was the basis for the GOAL (Gaining Optimal Asthma ControL) study (15). In this study, the investigators sought to determine if the goals of the current guidelines for optimal asthma control could be attained. The study evaluated the ability of an ICS alone or in combination with a long-acting beta-agonist (LABA) to achieve well-controlled and totally controlled asthma. A well-controlled subject could have asthma symptoms on two days out of an 8-week period but not more frequently. As seen in Table 3, the parameters that had to be met by all patients at all times were no nighttime awakenings, no exacerbations, no ER visits, or treatment related to adverse events. In addition, lung function had to be greater than 80% of predicted every day. Total asthma control was essentially a complete remission of asthma, having no symptoms present, and an FEV_1 of greater than 80% of predicted. The time line to gain asthma control in this study was tracked over a 52-week period (Figure 5) with dose of the inhaled glucocortoid (GC) in both groups escalated until total control was achieved or until the maximum dose was reached. For the combination salmeterol and fluticasone group, approximately 71% were able to have well-controlled asthma versus 59% in the fluticasone only group. Control was lower depending on the baseline severity of asthma as determined by medication needs (no inhaled steroid, medium-dose inhaled steroid, or high-dose inhaled steroid) at study entry. The dose escalation in this study reached 1, 000 μg per day of either single entity or in combination in 76% of the patient's receiving salmeterol/fluticasone and 68% of the fluticasone only patients. Despite high-dose fluticasone, total control was

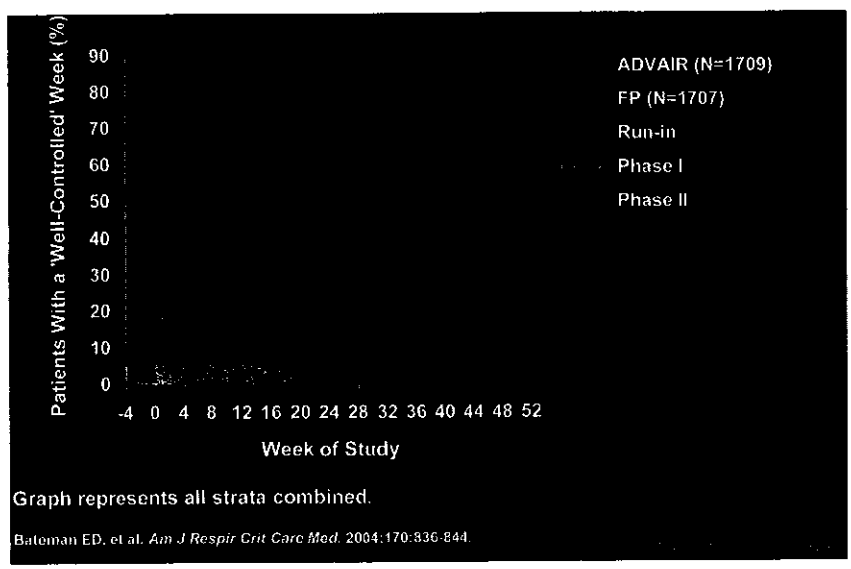

FIGURE 5.—Proportion of patients achieving a well-controlled week.

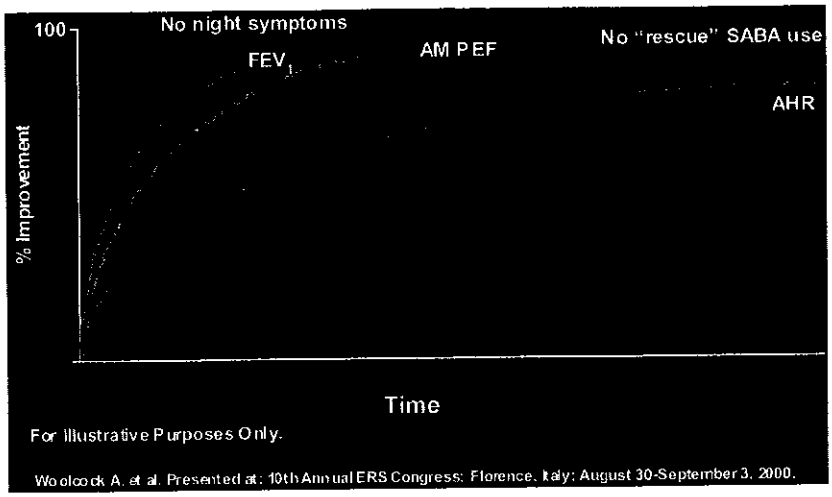

FIGURE 6.—Time course of achieving asthma control.

achieved in only 28% of the single entity and 41% of combination therapy after 1 year. Woolcock has described a time frame for achieving asthma control looking at a variety of variables as seen in Figure 6, with nighttime symptoms being the most responsive to therapy within days but taking months to years for bronchial hyperresponsiveness to improve.

TOOLS TO ASSESS ASTHMA CONTROL

Several questionnaires that assess composite measures of asthma control have been developed. These include the Asthma Control Test (ACT), the Asthma Therapy Assessment Questionnaire (ATAQ), and the Asthma Control Questionnaire (ACQ). All of them rely on daytime and nighttime symptoms in addition to rescue short-acting beta-agonist use (Table 4). The ATAQ allows for assessment of four dimensions of control: (1) the patient's perception of control; (2) missed work or school; (3) nighttime awakening due to asthma; and (4) use of short-acting beta-agonists for symptoms. It is scored on a 0 to 4 scale over a 4-week period. A patient with a score of zero has well-controlled asthma, while a patient with a score of 4 has active asthma with all 4 domains affected. The ACQ employs seven questions to determine level of control. These include (1) nocturnal symptoms; (2) morning symptoms; (3) activity limitation; (4) shortness of breath; (5) wheezing; (6) need for rescue beta-agonist; and (7) lung function impairment. This instrument utilizes a 1-week recall period and uses a seven-point scale (0 to 6) with 0 being complete control and 6 being very poor control. The ACT is the most recent instrument to be developed and uses five questions: (1) daytime symptoms; (2) nighttime symptoms; (3) rescue beta-agonist use; (4) daily activity limitation; and (5) patient's perception of control

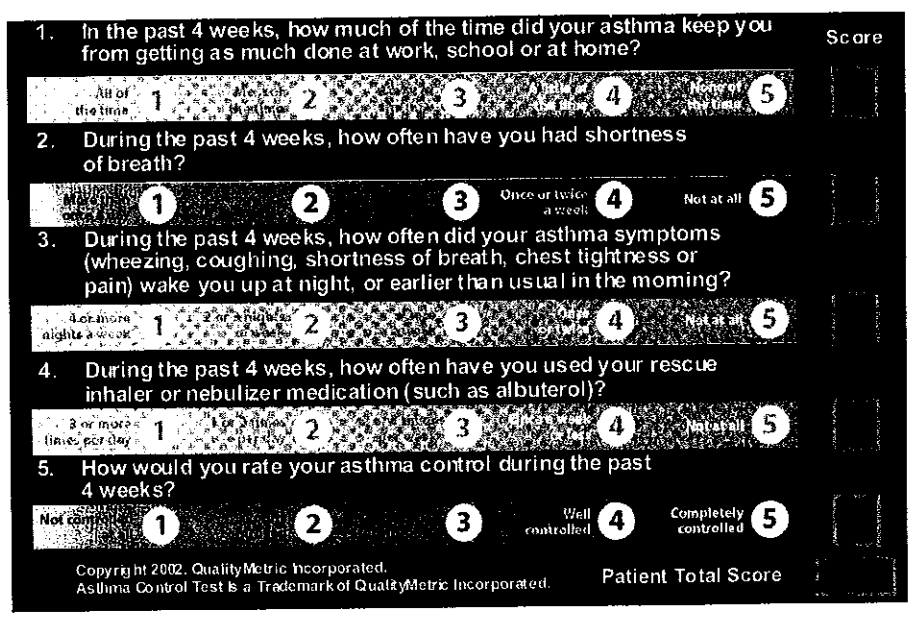

FIGURE 7.—Asthma control test™ (ACT).

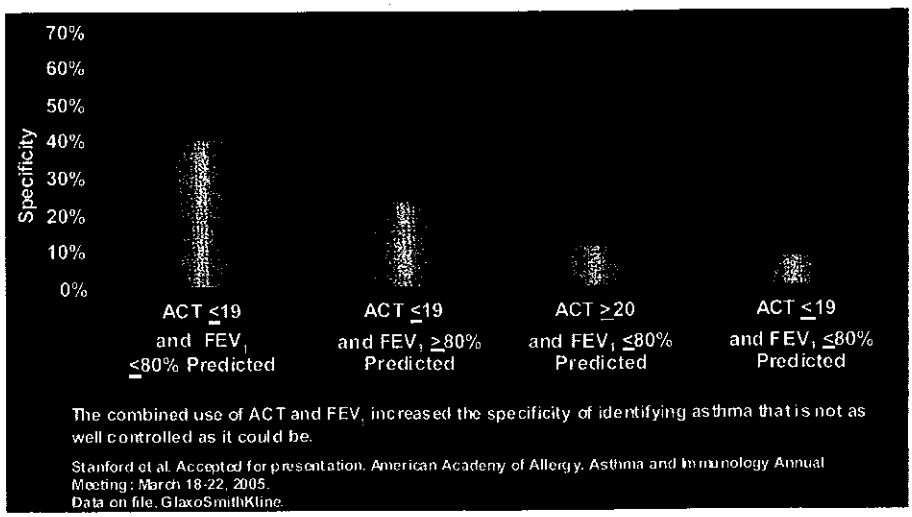

FIGURE 8.—Asthma status based on 2 measures of disease control.

(Figure 7). This instrument uses a 4-week recall period and uses a 5-point scale (1 to 5). A patient with a composite score of 25 would be in complete control, while a patient with a score of 5 would be in very poor control (Figure 8). The ACT questionnaire was validated in 313 patients before a visit to one of six asthma specialty groups (16). Pre-bronchodilator FEV_1 was obtained and the 5-point scale ranging from not controlled to completely controlled was used. At the end of the validation study, it was determined that a score of 19 or less predicted an FEV_1 of less than 80% predicted 43% of the time and also correlated with increasing asthma symptoms. An ACT of 20 or greater was considered reflective of good asthma control based on absence of symptoms, higher physician assessment of control, and normal lung function.

SUMMARY

Therefore, it is important to determine asthma control based on a multidimensional approach including physiologic assessment, global assessment of functionality, daytime symptoms, nighttime symptoms, healthcare utilization, and adherence to therapy.

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