Common measures of asthma severity lack association for describing its clinical course

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Background and Objective: *To address the problems of increasing asthma morbidity and mortality rates, reliable severity measures must be identified. Accordingly, we compared three measures and their relationship to beclomethasone compliance.*
Methods: *Three clinical measures (symptom scores, morning peak expiratory flow rates, and number of as needed albuterol inhalations with Nebulizer Chronologs [Forefront Technologies, Inc., Lakewood, Colo.]) were assessed daily in 13 adults with asthma for 8.9 ± 2.1 weeks. The relationships among these three variables were analyzed in terms of Pearson correlation coefficients. These were evaluated for each of the three possible pairs of the three clinical measures for each of the 13 patients. The relationship between inhaled beclomethasone compliance and the pairwise correlations was studied with the use of nonparametric statistical procedures.*
Results: *In four of the 13 patients, no pairwise correlations between any of the three severity measures were observed. The peak expiratory flow rate–symptom score relationship was observed in eight patients, whereas peak expiratory flow rate–albuterol use and albuterol use–symptom score correlations were each seen in four patients. Mean beclomethasone compliance was 64% and was greatest in those patients whose albuterol use increased concurrently with symptom scores (94% vs 50%, p = 0.02).*
Conclusions: *The commonly used measures of asthma severity, symptom scores, peak flow rate, and β-agonist use may not be interchangeable in describing the clinical course. Patients whose β-agonist use is driven by symptoms tend to be more compliant with use of inhaled corticosteroids. (J ALLERGY CLIN IMMUNOL 1994;94:732-7.)*

Key words: *Asthma, peak expiratory flow rate, inhaled albuterol, compliance, inhaled beclomethasone*

Because asthma morbidity and mortality rates are increasing,[1-3] reliable measures of asthma severity, both for individual patient evaluation and formal clinical investigation, are needed. Asthma severity has been measured by means of physician assessment, peak expiratory flow rate (PEFR), inhaled β-agonist requirement, daytime and nocturnal symptoms, and, in more severe cases, numbers of hospitalizations or emergency room visits, episodes of pneumothorax, pneumomediastinum, and intubation.[4-7]

Abbreviations used
NHBLI: National Heart, Lung, and Blood Institute
PEFR: Peak expiratory flow rate
prn: As needed

Particularly useful are those variables that are easily obtainable and therefore may be used routinely in outpatients to indicate an early exacerbation. In this study three of the most commonly used measures of asthma severity were evaluated: patient symptom report, PEFR, and as needed (prn) inhaled β-agonist use. Their interrelationships and association with beclomethasone compliance were determined.

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Symptom reports and PEFRs were used as recommended in current national guidelines[3] as a means of best understanding commonly used elements of patient assessment. Because patients of most concern to practitioners are those whose asthma is at least moderately severe, subjects were selected to fulfill the National Heart, Lung, and Blood Institute (NHBLI) criteria for moderate asthma.

METHODS

Subjects

Thirteen adult outpatients with asthma who met the American Thoracic Society criteria for asthma[8] were recruited. All had moderate asthma according to the NHLBI criteria,[3] but none were receiving maintenance oral corticosteroids when they entered the study. None had other significant pulmonary or medical diseases, were current smokers, or had smoked for more than a total of 10 pack-years. All patients' conditions were stabilized with inhaled beclomethasone and prn inhaled β-agonists for at least 30 days before the study period.

The study protocol was approved by the institutional review boards of the University of Connecticut Health Center and St. Francis Hospital and Medical Center. All subjects gave informed consent before participation.

Protocol

The study period was 9 weeks. During this time, patients were directed to use their inhaled beclomethasone regularly and their inhaled albuterol prn. The remainder of the medications were continued unchanged. Oral corticosteroids were added, when necessary, as recommended by the patient's physician.

Beclomethasone and albuterol canisters were placed in Nebulizer Chronologs (Forefront Technologies, Inc., Lakewood, Colo.),[9] devices that electronically store the time and date of each inhaler actuation. The exact function of these devices was not described to participants.

Beclomethasone compliance, which was calculated for each patient's daily use, was expressed as a percent of prescribed use, according to the following formula: compliance = (number of actuations recorded by the Chronolog ÷ prescribed number of actuations) × 100.

Symptoms of cough, wheeze, chest tightness, and dyspnea were graded daily by each patient and recorded in a diary format. Each of these symptoms was then converted to a numeric scale, ranging from 1 to 4, with 1 indicating no symptoms, 2 mild symptoms, 3 moderate symptoms, and 4 severe symptoms. Total daily symptom score therefore ranged from 4 to 16.

All subjects were instructed in the use of a peak flow meter according to NHBLI recommendations[3] at entry, and instructions were reviewed at subsequent visits. The PEFR was measured with an Assess Peak Flow Meter (Health Scan Products Inc., Cedar Grove, N.J.) and recorded each morning, before medication use, in the diary. Subjects were not blinded to PEFR results.

Physician visits were scheduled every 3 weeks. At these times, symptom, PEFR, and Nebulizer Chronolog use data were collected. The treating physician did not have access to these data at the time of examination.

Statistical analysis

The daily relationship of the three severity measures (PEFR, symptoms, and albuterol use) was evaluated for each patient with Pearson product moment correlation coefficients. Because there were three possible pairwise combinations of the three severity measures for each of 13 patients, a potential total of 39 parameters could be estimated. The correlations were calculated with daily data. Because patients were followed up for an average of 59.8 days, the effective sample size for estimating the correlation coefficients was relatively large, and the tests of significance of the correlations were reasonably powerful. However, given the number of parameters to be estimated, 0.03 was designated as the p value for determining whether an estimated coefficient was different from zero. Furthermore, the association between two variables was considered at least moderately strong if the corresponding correlation coefficient, r, was greater than 0.65 or less than −0.65.

The association between each pair of severity measures and beclomethasone compliance was evaluated by comparing two groups of patients. These patient groups were defined in terms of the significance of the association between each of the three pairs of severity measures: albuterol use and symptom score, PEFR and albuterol use, and symptom score and PEFR. The first group consisted of those patients for whom there was a significant association between one of the pairs of severity measures; the second group consisted of patients with no significant association. For example, patients who demonstrated a significant correlation between symptom scores and albuterol use were placed in one group, and those in whom such an association was absent were placed in the second group. Then, beclomethasone compliance was compared between these two groups. Next, two groups were formed on the basis of the presence or absence of a significant association between albuterol use and PEFR. Compliance between these two groups was compared. The Mann-Whitney U test was used to assess differences in beclomethasone compliance between these groups.

RESULTS

Data collection

Although the planned study period was 9 weeks, mean patient participation was 8.9 ± 2.1 weeks. One subject's participation (patient 13) ended after 4 weeks when he was hospitalized because of chest discomfort, which was eventually diagnosed as viral pericarditis. The Chronolog

TABLE I. Clinical characteristics of 13 subjects (3 men and 10 women)

Characteristic	Mean	Range
Age (yr)	43.5	23-66
Lifetime hospitalizations for treatment of asthma	4.7	0-20
Lifetime emergency room visits	8	0-30
Oral steroid use (no. of days/previous year)	77	0-300
Nocturnal awakenings in previous month	7.8	0-31

TABLE II. Clinical features during study period

Patient No.	Prescribed steroid (inhal/day)	Steroid compliance (%)	Mean PEFR (L/min)	Mean symptom score	Mean albuteral (inhal/day)
1	8	70 (12.5-175)	357 (220-550)	6.9 (5-10)	4.0 (0-14)
2	8	95 (75-125)	460 (310-660)	8.7 (8-12)	7.4 (4-17)
3	12	106 (75-183)	362 (300-410)	9.5 (8-12)	8.8 (4-13)
4	8	104 (75-162)	425 (370-460)	6.2 (4-11)	5.0 (0-14)
5	8	85 (50-137)	138 (110-180)	9.7 (6-16)	2.7 (0-10)
6	16	42 (0-100)	420 (350-530)	8.5 (8-11)	7.8 (0-28)
7	16	11 (0-56)	244 (140-330)	7.7 (4-12)	0.91 (0-6)
8	16	52 (0-106)	417 (230-750)	8.5 (4-14)	5.4 (0-21)
9	8	68 (0-112)	173 (100-250)	12.6 (8-16)	4.6 (0-9)
10	16	43 (0-112)	171 (100-200)	9.3 (8-11)	0.18 (0-4)
11	16	20 (0-75)	374 (340-470)	4.4 (4-8)	0.05 (0-4)
12	15	52 (0-213)	357 (300-470)	8.2 (4-12)	*
13	16	81 (75-125)	559 (500-600)	5.2 (4-16)	0.88 (0-11)

Numbers in parentheses represent ranges. The steroid used was inhaled beclomethasone. Steroid compliance was measured for each subject's daily use as the number of actuations recorded by the Chronolog divided by the prescribed number of actuations expressed as a percent. The mean of the daily compliance scores is reported in this table. Symptom score = Sum of scores for cough, wheeze, chest tightness, or dyspnea with each symptom graded from 1 to 4, where 1 indicates no symptoms; 2, mild symptoms; 3, moderate symptoms; and 4, severe symptoms. Therefore symptom scores range from 4 to 16.

Inhal, Inhalations.

*Missing data because of battery failure of Chronolog used for albuteral.

battery for the albuterol inhaler of patient 12 failed, but information on inhaled beclomethasone and patient diaries were obtained. Thirty-three days of albuterol records were lost for patient 8, and 20 days for patient 10 when those batteries failed. Patient 12 did not record her symptom scores on 13 days or her PEFR on 9 of the 39 days during which she participated. In all, there were 778 patient days of data collection.

Patients

The participants' initial clinical characteristics before the study are described in Table I. Four of the patients had never been hospitalized for treatment of asthma; the remainder had been admitted more than once. Another four patients had a history of at least 10 emergency room visits that did not lead to admission, as well as multiple hospitalizations for treatment of asthma. With the exception of one, all subjects had taken corticosteroids orally in the previous year, and 11 had received at least 30 days of the medication. All but four reported nocturnal awakenings caused by asthma symptoms in the month before entry.

Clinical features during the study period

The clinical courses of the patients during the study period are described in Table II. As indicated by the individual patient ranges, there was considerable variation in daily PEFR, symptom scores, and albuterol use. Five participants had clinical exacerbations requiring either the institution of or an increase in already prescribed corticosteroids.

Twelve of the subjects were prescribed beclomethasone in dosing regimens of four times a day.

TABLE III. Beclomethasone compliance and pairwise correlations of three measures of asthma severity

Patient No.	Steroid compliance (%)	PEFR and symptoms		Albuterol and symptoms		PEFR and albuterol	
		r	*p*	*r*	*p*	*r*	*p*
1	70	0.27	0.03	−0.11	0.38	−0.27*	0.03*
2	95	0.012	0.92	0.15	0.24	−0.23	0.07
3	106	−0.58*	0.001*	0.41*	0.0009*	−0.13	0.31
4	104	−0.54*	0.0001*	0.62*	0.0001*	−0.33*	0.009*
5	85	−0.38*	0.003*	0.34*	0.008*	−0.30*	0.02*
6	42	0.20	0.11	−0.02	0.84	−0.21	0.10
7	11	−0.12	0.31	−0.07	0.57	−0.10	0.44
8	52	−0.44*	0.0008*	0.13	0.55	−0.20	0.36
9	68	−0.27*	0.03*	0.15	0.25	−0.23	0.06
10	43	−0.022	0.86	0.009	0.95	−0.05	0.74
11	20	−0.48*	0.0001*	−0.05	0.67	−0.06	0.57
12	52	−0.59*	0.002*	†	†	†	†
13	81	−0.52*	0.01*	0.94*	0.0001*	−0.48*	0.02*

r, Correlation coefficient; *p*, *p* value.
*Significant pairwise correlations. A correlation was considered significant if $p \leq 0.03$. The strength of the correlation was believed to be at least moderately strong if $r \leq -0.65$ or $r \geq 0.65$.
†Missing data resulting from battery failure of the albuterol Chronolog.

The remaining subject, a graduate student with an irregular schedule, was prescribed 15 actuations a day in any schedule convenient for her. The mean of individual mean daily beclomethasone compliance was 64%.

Correlations between measures of asthma severity

Pairwise severity measure correlations for all 13 subjects are displayed in Table III. The relationship between PEFR and symptom score for patient 1 was not considered significant because the correlation coefficient was positive rather than negative (i.e., symptoms improved as PEFR decreased). Albuterol data were missing in one patient (patient 12); hence, two of the possible 39 correlation coefficients could not be estimated.

Sixteen of the 37 possible correlations were considered significant (i.e., statistically different from zero). None of these were considered strong, except for the symptom score–albuterol use association for patient 13. The PEFR–symptom score relationship was most commonly observed (eight patients). No significant pairwise correlations were observed in four patients.

Fig. 1, *A* and *B* shows daily prn albuterol use, symptom scores, and PEFR in two subjects; one, patient 4, had concordance in all three measures, and the other, patient 10, had no concordance for any severity measures.

Compliance and measures of asthma severity

Severity measures taken singly were not associated with beclomethasone compliance; that is, neither albuterol use, nor PEFR, nor symptom scores alone were associated with beclomethasone compliance. However, patients whose albuterol use increased concurrently with symptoms were more compliant with use of inhaled beclomethasone than were those in whom the association was lacking (94% vs 50%, $p = 0.02$).

DISCUSSION

The difficulties experienced by both patients and their physicians in recognizing asthma severity may be one explanation for the increase in morbidity and mortality rates from this illness.[3,4,10-15] In an effort to improve the detection and treatment of asthma, the NHLBI has proposed management guidelines for measuring asthma severity, which advocate the use of PEFR and symptom diaries.[3] In addition, prn inhaled β-agonist requirement reflects asthma severity.[3, 16] The purpose of this study was to evaluate the interrelationships of these three commonly endorsed measures of asthma severity as they are routinely used by outpatients with moderate asthma.

Unexpectedly, the anticipated strong associations between prn albuterol use, PEFR, and symptom scores were not present in these pa-

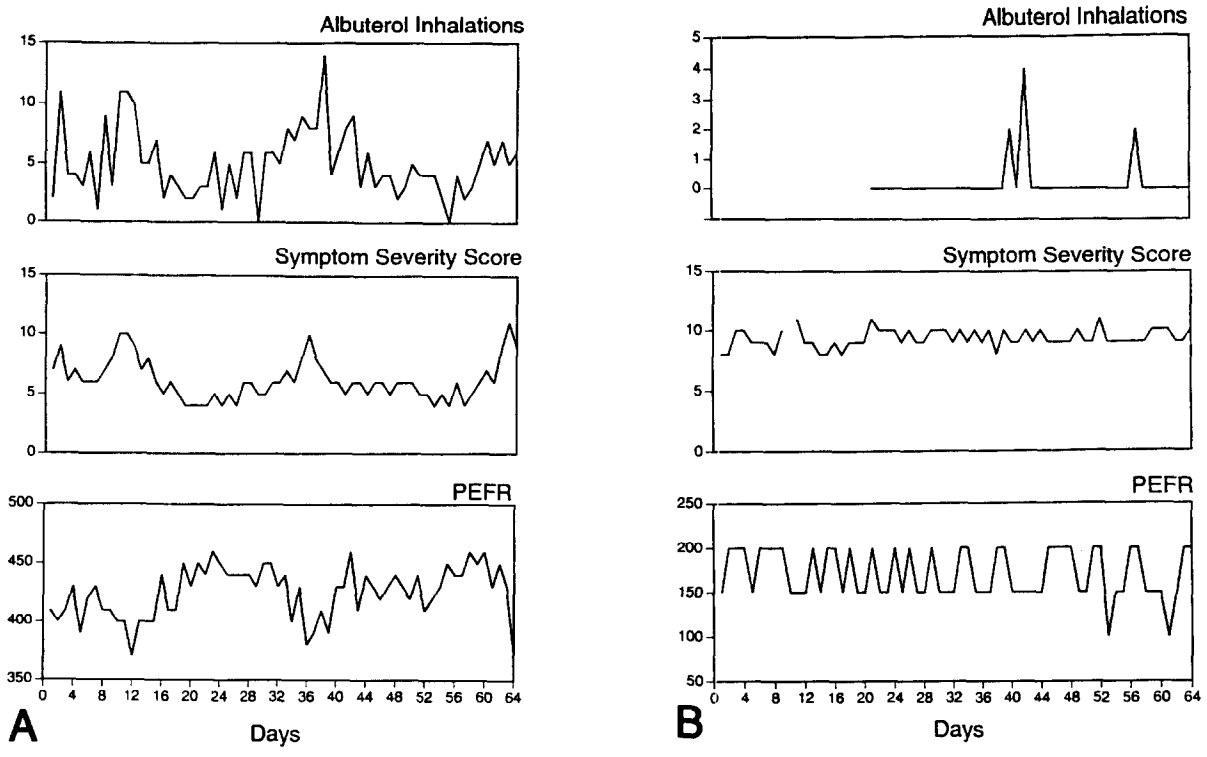

FIG. 1. As needed (prn) albuterol use, symptom scores, and PEFR in two subjects. **A,** Severity measures for patient 4, who had concordance in all three pairs of severity measures. **B,** Data for patient 10 for whom there was no concordance for any pair of severity measures. Chronolog failure resulted in loss of some data on albuterol use for this patient. Note the differences in scale between patients 4 and 10 with respect to albuterol actuations and PEFR.

tients. Thus statistically significant pairwise correlations were absent in four patients and generally weak in the remaining nine patients. Discrepancies in asthma severity measurement have been noted before,[10, 12, 15] leading to the suggestion that use of only one indicator may underestimate asthma severity.[7]

It is possible that some subjects, such as patient 1 whose PEFRs decreased with improving symptoms, either did not use the meters correctly or marked down symptom scores at random. However, participants were given instructions in a standard manner according to accepted guidelines.[3] It was our intent to use these severity measures as recommended by clinicians in order to assess the ability of these measures to provide information.

Three other factors may contribute to the disparity in these severity measures: (1) patient variability in perceiving airway obstruction, (2) temporal bias in obtaining these measures, and (3) bias from unblinded PEFR recordings obtained concurrently with symptom reports.

Properly performed, the PEFR objectively measures underlying airway obstruction. Symptom recording and prn albuterol use, on the other hand, require perception of that obstruction. Because some patients with asthma are unable to detect severe increases in airway obstruction during bronchoprovocation[17] and others are not able to recognize the overall severity of their disease,[18] this clinical PEFR-symptom discrepancy is not surprising. This discrepancy has been noted by others,[10, 19] although not compared with albuterol use or compliance. Our subjects in whom PEFR and symptoms were correlated were not more compliant with beclomethasone and did not use albuterol more frequently, indicating that the correlation between PEFR and symptoms does not fully explain perception of disease state.

In this study PEFR and symptom scores were recorded in the morning, whereas albuterol actuations were recorded throughout the day. Hence, morning asthma symptoms may have influenced the first two variables to a greater degree than albuterol requirement. Interestingly, the

most frequently observed pairwise association was between PEFR and symptom scores, possibly reflecting this temporal bias. It is likely that the best clinical tools for understanding fluctuations in asthma will be those in which data collection occurs throughout the day and night rather than at one time point with several severity measures.

Finally, there may have been an unconscious tendency for the patient to make PEFR and symptom scores consistent because they were recorded at approximately the same time. Indeed, the PEFR-symptom concordance, which was present in eight of the 13 patients, was most frequent in this group. Blinding of PEFR, which is not possible with conventional peak flow meters, would eliminate this potential bias.

Although inhaled corticosteroids are considered the foundation in the treatment of moderate asthma, compliance with these prophylactic medications in this group was a disappointing 64%, a finding not dissimilar to results of previous work.[20, 21] In other words, subjects on average took only a little more than half of the prescribed medication. If compliance with inhaled corticosteroids is defined, as it is by Mawhinney et al.,[20] as taking at least 75% of the prescribed inhalations, only five subjects (38%) could be considered compliant. These findings suggest either the inadequacy of patient education or the importance of lack of perception of symptoms for many patients. Significantly, those individuals who responded to increasing symptoms with increased albuterol use were more compliant with use of inhaled beclomethasone.

In summary, the commonly used measures of asthma severity—symptom scores, peak flow rate, and β-agonist use—may not be interchangeable in describing the clinical course of asthma, especially asthma that is moderate to severe. Patients whose β-agonist use is driven by symptoms tend to be more compliant. Better understanding of asthma severity measures may allow better identification of those subjects who do not recognize the magnitude of their disease.

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