Assessing Symptoms and Peak Expiratory Flow Rate as Predictors of Asthma Exacerbations

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OBJECTIVE: To investigate peak expiratory flow rate (PEFR) and quality of life scores for their ability to predict exacerbations of asthma.

PARTICIPANTS AND METHODS: We identified adults who received oral or inhaled asthma medications from 36 community drugstores. We administered the McMaster Asthma Quality of Life Questionnaire (AQLQ) and measured PEFR, defining "red zone" (highest risk) as a PEFR < 50% of each patient's expected value based on gender, age, and height. We identified asthma exacerbations (breathing-related emergency department visits and hospitalizations) within 4 and 12 months after enrollment and used proportional hazards regression to assess the ability of PEFR and AQLQ scores to predict exacerbations, controlling for clinical and demographic factors.

RESULTS: A red zone PEFR was a significant univariable predictor of exacerbations within 12 months (hazard ratio [HR], 1.8; 95% confidence interval [CI], 1.1 to 3.0; $P = .027$). However, neither a red zone PEFR, the raw PEFR, or percent of predicted maximal PEFR were significantly predictive when controlling for AQLQ scores, clinical characteristics, or demographic data ($P > .2$). However, the 4 subscales of the AQLQ were each significant univariable and multivariable predictors of asthma exacerbations. For example, the overall AQLQ scale had a multivariable HR of 0.63 (95% CI, 0.46 to 0.87; $P = .005$) for exacerbations occurring within 4 months and 0.66 (95% CI, 0.54 to 0.82; $P < .001$) within 12 months.

CONCLUSIONS: PEFR added no predictive information to that contained in AQLQ scores and clinical and demographic data. These results support the National Institutes of Health asthma guidelines' recommendation for routinely assessing symptoms but not PEFR.

KEY WORDS: asthma; peak expiratory flow rate; symptoms; quality of life.

J GEN INTERN MED 2004;19:237-242.

Asthma affects more than 4% of the adult population in the United States, and its prevalence is rising.^{1,2} In 1995, more than 1.5 million emergency department visits and 500,000 hospitalizations were attributable to asthma in the United States. In 1998, hospitalizations alone accounted for approximately 48% of the estimated \$7.5 billion in direct costs for asthma in the United States.³ Available medical therapies can prevent or reduce the complications of asthma, including asthma-related emergency department visits and hospitalizations.⁴⁻⁹

Peak expiratory flow meters are inexpensive and convenient devices that provide reproducible, objective measurement of lung function.¹⁰ While current asthma guidelines recommend routine assessments of peak expiratory flow rate (PEFR) and symptoms for outpatient management of patients with asthma,¹¹ the ability of these measures to predict asthma exacerbations is unknown. While current guidelines also recommend monitoring symptoms and their impact on patients, the clinical value of validated asthma-specific quality of life questionnaires¹² as a mechanism to assess the impact of disease and predict exacerbations is also unknown.

In an attempt to provide novel data on the clinical value of these 2 recommended monitoring parameters, we investigated the ability of measurements of PEFR and an asthma-specific symptom and quality of life assessment instrument to predict asthma-related emergency department visits and hospitalizations.

METHODS

This study was approved by the Indiana University-Purdue University at Indianapolis Institutional Review Board. The data were gathered as part of a randomized, controlled trial of a comprehensive pharmaceutical care intervention that has been described previously.^{13,14} A brief summary is provided below.

Setting and Randomization

The trial was conducted in 36 commercial drug stores in Indianapolis and had an intervention group and 2 control groups. The 36 study stores were stratified into 12 clusters of 3 stores (triplets); the 3 stores within each triplet were matched on geographic proximity, the percent of adults with reactive airways disease who had Medicaid (to control for socioeconomic status), and the number of prescriptions filled (high- vs low-volume stores). Within triplets, stores were randomly assigned to each of 3 study groups. Patients in the *pharmaceutical care intervention group* received a peak flow meter and personalized instruction about its use. Patients in the *PEFR monitoring control*

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group did not receive the pharmaceutical care intervention but did receive a peak flow meter and instructions about its use. Patients in the *usual care control group* received neither the intervention nor routine assessment of PEFr.

Patient Selection

Potential subjects were patients visiting the 36 study drugstores who had filled prescriptions for a breathing medication (methylxanthines, inhaled corticosteroids, inhaled or oral sympathomimetics, inhaled parasympathetic antagonists, leukotriene pathway modifiers, or inhaled cromolyn) in the past 3 months. The national office of the drugstore chain mailed 14,195 letters to potential subjects identified from their prescription database, inviting them to voluntarily participate in a program to improve the health of its customers. Patients agreeing to be contacted returned a signed form authorizing the drugstore chain to release their names to the study's project manager who contacted them by telephone to assess their eligibility. Patients were eligible if they were at least 18 years old, were currently taking 1 of the asthma medications listed above, filled at least 70% of their prescriptions at a single drugstore in this chain, and agreed that they had an active breathing problem. Patients were ineligible if they were institutionalized or had significant impairment in speech, vision, or hearing that prevented their being interviewed. Of the 2,951 patients who returned a form indicating interest in the study, 136 (5%) could not be contacted, 1,201 (41%) were ineligible, 492 (17%) were eligible but refused to participate in the trial, and 8 were included in a pilot study and excluded from the main study. Of the 1,113 (38%) who agreed to participate and were enrolled, 660 had asthma by virtue of *not* having chronic obstructive pulmonary disease as defined by the American Thoracic Society: being both older than 45 years old and having a significant prior smoking history (≥ 10 pack/year equivalent).^{9,15}

Intervention

Pharmacists at all stores received education regarding pharmaceutical care. Pharmacists practicing in intervention drugstores received instructions for assessing and managing reactive airway disease and orientation to intervention educational materials and study computers. When an enrolled patient visited an intervention drugstore and filled a prescription (not necessarily for their breathing problem), the drugstore's computer prompted the pharmacist to access patient-specific data sent nightly to a special study computer. These data included PEFr (obtained at enrollment and during monthly interviews), dates of recent emergency department and hospitalization visits, active breathing medications, each with refill history and medication compliance score,¹⁶ and how to contact the subject's primary care and pulmonary physicians.

Intervention pharmacists were encouraged to provide counseling and educational materials to patients and to contact the subject's physician based on their judgment or

in accordance with detailed, problem-based intervention resource guides. Pharmacists practicing in control drugstores received no information about enrolled patients filling prescriptions, beyond that contained in the drugstore's computer system, and had no access to the paper or electronic intervention materials.

Data Collection

At enrollment, 6 months, and 12 months, each patient had a face-to-face interview with a trained interviewer who administered the McMaster Asthma-Specific Quality of Life Questionnaire (AQLQ)^{17,18} and measured PEFr. Following randomization, subjects in all 3 study groups were telephoned monthly and asked about recent emergency department visits and hospitalizations. To the best of their ability, they provided their reasons for making these visits. Data for subjects' emergency department visits and hospitalizations (date and discharge diagnoses) were also obtained from a city-wide computer network into which all major Indianapolis hospitals send data on emergency department visits and hospitalizations.¹⁹ In all instances, interviewers were unaware of patients' prior data or their study group assignment.

Patients in the intervention group and PEFr monitoring control group provided PEFr readings during the enrollment interview and each monthly telephone interview using a Personal Best portable device (Health Scan Product, Inc., Cedar Grove, NJ) that was handed to them during the enrollment interview. The maximum expected PEFr value for each enrolled patient was calculated using curvilinear models based on gender and assuming effect for age and height.²⁰ Whenever possible, PEFr measurements were taken with subjects standing (97%). The best of 3 separate attempts was recorded. We divided this value by the maximal expected PEFr to obtain the percent of maximum PEFr, which was further categorized into 3 "zones": red (<50% predicted maximum PEFr), yellow (50% to 80% of predicted maximum PEFr), and green (>80% of predicted maximum PEFr).

The AQLQ^{17,18} contains 32 items in 4 subscales (activity limitations caused by asthma, asthma-related symptoms, environmental stimuli, and emotional function). Patients must recall the impact of their asthma during the previous 4 weeks. Item responses contain a 7-point Likert scale that ranges from a score of 1 (worst) to 7 (best). Subscales are scored by taking the mean of each completed item in that subscale. The overall score is the mean of all 32 AQLQ items.

Outcome Variables and Statistical Analyses

Two of the investigators (MDM and WMT), blinded to all other patient data and study group assignment, separately reviewed information on each emergency department visit and hospitalization gathered from the patients' monthly telephone interviews and computerized hospital records. They independently assessed whether a visit was

an "asthma exacerbation" defined as a emergency department or hospital discharge diagnosis of asthma, reactive airways disease, or lower respiratory infection (bronchitis or pneumonia). All differences of opinion were discussed and adjudicated.

To assess the ability of enrollment PEFR and AQLQ scores to predict subsequent asthma exacerbations, we used proportional hazards (Cox) regression.²¹ The dependent variable was the number of days between baseline data collection and the first asthma exacerbation, censoring exacerbation data at 365 days. To evaluate the ability of baseline PEFR and AQLQ scores to predict more near-term exacerbations, we repeated this analysis after censoring the outcome data at 4 months (120 days) after baseline data collection.

We first performed univariable proportional hazards regression for each of 3 manifestations of the PEFR (actual value, percent of predicted maximum PEFR, and PEFR in the red zone vs yellow zone vs green zone, as defined above), each of the 4 AQLQ subscales (activities, symptoms, emotion, and environment), and the overall AQLQ scale. We then included significant ($P < .05$) univariable predictors in the multivariable proportional hazards regression analysis. Among the 3 manifestations of the PEFR, we included only the strongest univariable predictor in the final multivariable model. Because the AQLQ subscales and overall scale were highly correlated with each other, a priori we decided to include only the overall AQLQ scale (if significant univariably) in the multivariable analyses. To adjust for recent asthma activity prior to enrollment and patients' tendency to use emergency rooms, in all multivariable analyses we included a variable indicating whether an asthma exacerbation had occurred within 30 days prior to baseline.

Enrolled patients in the 3 study groups were similar except for race ($P = .005$). For this reason, all analyses control not only for study group, but also for race. To control for demographic and geographic differences among study participants, we also included the randomization drug store triplet in all multivariable analyses.

We used Wald's χ^2 test²¹ to test statistical significance of explanatory variables in the Cox analyses. P values of less than .05 were considered statistically significant. We employed Kaplan-Meier estimates²¹ to produce survival curves. S-plus (Math Soft, Inc., Seattle, Wash) and SAS (SAS Institute, Cary, NC) were used for all statistical analyses.

RESULTS

Population Characteristics

The mean age of enrolled patients was 45 years; the majority were white women. The mean baseline PEFR was 351 l/min (range 70 to 710), 71% of the maximum value predicted based on gender, age, and height.²⁰ Asthma Quality of Life Questionnaire subscales showed that patients' symptoms moderately impaired their quality of life (mean subscale scores of 4.3 to 4.6 on a 7-point Likert scale). During the month prior to enrollment, 22 (3%) of the subjects

Table 1. Subjects' Baseline Characteristics and Follow-up

Patients with asthma, N	660
Mean age, y $\pm$ SD	45 $\pm$ 15
Race	
White, n (%)	531 (81%)
Black, n (%)	113 (17%)
Other (Asian, Hispanic, Indian, other/unknown), n (%)	16 (2%)
Female, n (%)	539 (82%)
Mean education, y $\pm$ SD	14 $\pm$ 3
Asthma-related* emergency department visit or hospitalization in the month prior to enrollment, n (%)	22 (3)
PEFR, [†] mean l/min $\pm$ SD	351 $\pm$ 110
Percent of predicted PEFR, mean $\pm$ SD	71 $\pm$ 18
PEFR zone: green (PEFR $\geq$ 80%), n (%)	209 (32%)
PEFR zone: yellow (PEFR 50%–80%), n (%)	362 (55%)
PEFR zone: red (PEFR < 50%), n (%)	89 (14%)
Asthma Quality of Life Questionnaire, mean item score $\pm$ SD	
Activity limitations scale	4.6 $\pm$ 1.2
Symptoms scale	4.4 $\pm$ 1.2
Emotion scale	4.3 $\pm$ 1.4
Environment scale	4.3 $\pm$ 1.5
Overall scale	4.4 $\pm$ 1.2
Follow-up, mean number of months, range	11, 0 to 14

* Asthma-related was defined as an emergency department visit or hospitalization for asthma or lower respiratory illness.^{17,18}

[†] PEFR, peak expiratory flow rate.

had an asthma exacerbation. During an average follow-up period of 11 months (range 0 to 14), 87 of the subjects (13%) experienced at least 1 asthma exacerbation, 40 of which occurred in the first 4 months after enrollment. See Table 1.

Univariable Analyses

Neither the raw value of the PEFR nor the percent of predicted maximum PEFR were significant univariable predictors of asthma exacerbations within either 4 months or 12 months of baseline data collection (P values of .086 and .075, respectively). However, compared to readings in the yellow or green zone, an enrollment PEFR in the red zone was a significant univariable predictor of asthma exacerbations within 12 months of enrollment ($P = .27$) but not within 4 months of enrollment ($P = .36$). See Table 2.

Each of the enrollment AQLQ subscale scores, as well as the overall AQLQ score, were significantly predictive of asthma exacerbations at both 4 months ($P < .005$) and 12 months ($P < .001$).

Multivariable Analyses

Though predictive univariably, having an enrollment PEFR in the red zone was not a significant multivariable predictor of asthma exacerbations at 4 months ($P = .8$) or 12 months ($P = .2$). However, a lower score on the overall subscale of the AQLQ was a strong multivariable predictor of asthma exacerbations within 4 months ($P = .005$) and 12 months of enrollment ($P < .001$). Similar results were

Table 2. Univariable Predictors of Breathing-related Emergency Department Visits or Hospitalizations*

	Hazard Ratio [†]	Confidence Interval (95%)	P Value
4-Month follow-up			
Peak expiratory flow rate			
Actual value	1.0	0.99 to 1.0	.086
Percent of predicted	0.99	0.99 to 1.0	.075
Red zone (<50% predicted)	1.4	0.66 to 3.1	.360
Asthma Quality of Life Questionnaire [‡]			
Activities	0.55	0.41 to 0.75	< .001
Symptoms	0.64	0.48 to 0.84	.002
Emotion	0.70	0.56 to 0.87	.002
Environment	0.72	0.57 to 0.91	.005
Overall	0.56	0.41 to 0.76	< .001
12-Month follow-up			
Peak expiratory flow rate			
Actual value	1.0	1.0 to 1.0	.200
Percent of predicted	0.99	0.98 to 1.0	.220
Red zone (<50% predicted)	1.8	1.1 to 3.0	.027
Asthma Quality of Life Questionnaire [‡]			
Activities	0.62	0.50 to 0.75	< .001
Symptoms	0.68	0.57 to 0.82	< .001
Emotion	0.72	0.62 to 0.84	< .001
Environment	0.73	0.62 to 0.85	< .001
Overall	0.61	0.49 to 0.75	< .001

* Separate Cox's proportional hazards regression analysis of time to first emergency department visit or hospitalization controlled for race, intervention group, and pharmacy triplet (data from a pharmaceutical intervention study^{13,14}).

[†] Hazard ratio is for every 1.0 unit change.

[‡] Asthma Quality of Life Questionnaire score = McMasters Asthma Quality of Life Questionnaire with 4 distinct subscales (range 1 to 7; low is worse quality of life); overall score is average of Asthma Quality of Life Questionnaire score subscales.^{17,18}

obtained in multivariable analyses including the activities or symptoms subscales (data not shown). Having had an asthma exacerbation in the month prior to enrollment was also a strong independent predictor of subsequent asthma exacerbations within 4 months ($P < .001$) and 12 months of enrollment ($P < .001$). Figure 1 shows the Kaplan-Meier curve for overall AQLQ scores in the low (less than 4; $n = 212$), moderate (4.0 to 5.0; $n = 229$), and high ranges (greater than 5; $n = 219$). A patient with overall AQLQ scores of greater than 5.0 was almost 3 times more likely to have an asthma exacerbation during the year following enrollment than a patient with a score of less than 4.0. See Table 3.

DISCUSSION

The National Institutes of Health (NIH) guidelines for assessing and treating asthma suggest that clinicians routinely measure PEF and inquire about symptoms.¹¹

However, our prospective study in asthma patients receiving care in community-based drugstores found that an isolated measurement of PEF (whether represented by the actual value, percent of expected PEF, or PEF in the red zone) did not predict subsequent asthma exacerbations. Conversely, we found that a measure of asthma-related quality of life was a strong predictor of asthma exacerbations, supporting the NIH recommendations for assessing symptoms and their impact on patients.

Although the AQLQ has been used for assessing the outcomes of clinical trials for asthma therapies,^{12,22} its utility for assessing patients in everyday clinical practice has not previously been demonstrated.²³ Nonetheless, there are several components of these quality-of-life measurements that make them germane to every clinical evaluation. They quantify relevant clinical aspects of asthma, such as patients' symptoms and their effects on patients over a period of time (for the AQLQ, the 4 weeks prior to enrollment). The hazard ratio for the overall scale score of the AQLQ at the 4-month analysis (0.56 in Table 2) represents a 22% reduction in risk of having an asthma exacerbation for each one-half unit decrease in the overall scale score, a score change that has been shown to be clinically meaningful.²⁴ Therefore, the current study supports the clinical use of formal assessments of symptoms and asthma-related quality of life to identify high-risk patients who may be appropriate targets for risk-reducing interventions.

Although we did not find PEF to be predictive of subsequent asthma exacerbations, this does not mean that they have no role in asthma care. In the clinical trial of pharmaceutical care that formed the database used in this study, the group of patients who monitored their PEFs monthly had significantly higher PEFs at 12 months than

FIGURE 1. Time to first asthma-related emergency visit or hospitalization by overall quality of life score. Plot is a survival curve. The solid line represents patients with an overall scale score less than 4 ($n = 212$). The dotted line represents patients with overall scale scores of 4.0 to 5.0 inclusive ($n = 229$). The broken line represents patients with an overall scale score of greater than 5 ($n = 219$). Censored observations are indicated by "+".

Table 3. Multivariable Predictors of Asthma-related Emergency Department Visits or Hospitalizations*

	Hazard Ratio [†]	Confidence Interval (95%) [‡]	P Value
4-Month follow-up			
Red zone (<50% predicted)	1.1	0.52 to 2.4	.8
Overall Scale of the Asthma Quality of Life Questionnaire score [‡]	0.63	0.46 to 0.87	.005
Asthma-related emergency department visit or hospitalization in the month prior to enrollment	5.0	1.9 to 13	< .001
12-Month follow-up			
Red zone (<50% predicted)	1.4	0.86 to 2.4	.2
Overall Scale of the Asthma Quality of Life Questionnaire score	0.66	0.54 to 0.82	< .001
Asthma-related emergency department visit or hospitalization in the month prior to enrollment	3.8	1.8 to 7.9	< .001

* First emergency department visit or hospitalization for asthma or lower respiratory infection, controlled for intervention group and pharmacy triplet (data from a pharmaceutical intervention study^{13,14}).

[†] Hazard ratios and confidence intervals for peak expiratory flow measurements are for every 10 l/min change.

[‡] Overall Asthma Quality of Life Questionnaire score = average of all 4 Asthma Quality of Life Questionnaire subscales (range 1 to 7; low is worse quality of life).^{17,18}

control patients who did not measure their PEFR.¹⁴ Repeated assessments of PEFR may also be valuable in assessing changes from patients' baseline value. Repeated assessments of PEFR may aid patients in self-management of their asthma and is a routine part of many self-management programs, although evidence in clinical trials of its effectiveness even in self-management programs is lacking for adults^{25,26} and children.^{26,27} However, even single PEFR measurements may be useful in helping patients and their physicians improve patient management and optimal functional status. More research in this area is needed.

Limitations

There are 5 limitations to this study. First, as stated above, this manuscript represents a secondary analysis of data from a clinical trial, and caution should be used when making interpretations of analyses other than those for which the data were originally intended. Not all data that would be relevant to a prospective study of this nature were collected, such as socioeconomic status, intensity of treatment, frequency of nonemergency physician visits, and other characteristics of patients' ongoing care. Also, this was a study of baseline data only; the effects of subsequent treatment (which was the focus of the clinical trial) were not addressed in these analyses. However, we controlled for study group assignment and included the randomization scheme (which partially controlled for socioeconomic status) in our multivariable analyses.

Second, our study population was comprised of volunteers, a minority of all CVS Pharmacy patrons who were potentially eligible. Consequently, our subjects included a disproportionately low representation of the ethnic groups (i.e., nonwhite) who are at highest risk of asthma exacerbations, and had a disproportionately high number of women.¹ For this reason, our findings may not be generalizable to the broader population of persons with asthma.

Third, our definitions of asthma and asthma exacerbations were arbitrary. Defining asthma depended on subjects' receiving breathing medications, confirming that they had a "breathing-related illness," and having a smoking history of less than 10 pack years or age less than 45. We feel that our excluding persons over age 45 with greater than 10 pack years' smoking history was conservative. While it may have excluded from our analysis some patients with asthma, it was relatively unlikely to include patients who had chronic obstructive lung disease. Our definition of asthma exacerbations relied on emergency department and hospital discharge diagnoses made by treating physicians and included lower respiratory tract infections, which could occur in absence of bronchospasm.

Fourth, although we found the overall score of the AQLQ to be a highly significant independent predictor of asthma exacerbations, emergency department visits and hospitalizations for breathing-related problems may be relatively insensitive and/or nonspecific markers of patients having significant problems with their asthma. For example, patients suffering significant problems with their breathing may not seek urgent care, while emergency department visits "for asthma" may occur for reasons other than acute illness, such as medication refills, or for dyspnea caused by conditions other than asthma (e.g., heart failure). A study with a more sensitive and/or specific indicator of asthma complications may show the PEFR to be a better predictor.

Fifth, despite our having a standard protocol and trained technicians for measuring PEFR, many PEFR measurements may have been unreliable, thus limiting their predictive power. Also, PEFR is less sensitive for detecting obstruction of medium-sized airways and is more variable than the measurement of FEV1 for patients with asthma.¹¹ Our study therefore does not necessarily obviate the outpatient use of spirometry or formal pulmonary function testing, which might provide useful information beyond that provided by peak flow monitoring. However, our study

used a widely available peak flow meter in a standard manner that was consistent with the current NIH guidelines to routinely assess peak flow. The resulting PEFr measurements were not helpful in predicting which patients would need urgent care.

Future Directions

Clinical research should continue to assess the clinical utility of outpatient pulmonary function testing. Spirometry testing should be compared with PEFr to compare their predictive capabilities, and repeated pulmonary function measures should be studied to assess their utility in patient management.

The results from this study also provide rationale for future clinical investigations into using disease-specific quality-of-life measurements in the everyday clinical care of patients with asthma. Because they describe both the current impact of asthma on patients' health-related quality of life and their risk of adverse events, instruments such as the AQLQ should be studied to better define their role in asthma evaluation and management strategies.

This study was supported by grant HS-09083 from the Agency for Healthcare Research and Quality. Dr. Roesner was supported by training grant T32-HL07774 from the National Heart, Lung, and Blood Institute.

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