Predicting future risk of asthma exacerbations using individual conditional probabilities

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Background: Determination of future risk of exacerbations is a key issue in the management of asthma. We previously developed a method to calculate conditional probabilities (π) of future decreases in lung function by using the daily fluctuations in peak expiratory flow (PEF).

Objective: We aimed to extend calculation of π values to individual patients, validated by using electronically recorded data from 2 past clinical trials.

Methods: Twice-daily PEF data were analyzed from 78 patients with severe (study A) and 61 patients with poorly controlled (study B) asthma. For each patient, the π value was calculated from 5000 PEF data points simulated based on the correlation and distribution properties of observed PEF. Given an initial PEF, the π value was defined as the probability of a decrease in PEF to less than 80% of predicted value on 2 consecutive days within a month. These probabilities were then compared with actual occurrences of such events and clinically defined exacerbations within the following month.

Results: π Values were related to actual occurrences of decreases in PEF (adjusted $R^2 > 0.800$ for both studies). Every increase of 10% in π value was associated with an odds ratio of having a future exacerbation of 1.24 (95% CI, 1.07-1.43) for study A and 1.13 (95% CI, 1.02-1.26) for study B, with better sensitivity and specificity than clinic-measured FEV_1.

Conclusion: These results from 2 independent datasets with differing asthmatic populations and differing exacerbation criteria provide support that clinically relevant quantification of individual future risk of exacerbations is possible. (J Allergy Clin Immunol 2011;127:1494-502.)

Key words: *Peak expiratory flow rate, pulmonary function tests, patient monitoring, risk assessment*

Recent guidelines have highlighted the importance of determining future risk of deterioration in the management of asthma.[1,2] Monitoring strategies exist to assess asthma severity and control, but it is notoriously difficult to predict exacerbation risk.[2-5] The latter is important not only in the quality of life for the patient but also crucially influences treatment strategies. Several studies have identified lung function as an independent predictor of subsequent asthma exacerbations.[6-8] However, although current levels of lung function and other measures, such as symptoms, airway hyperresponsiveness, and exhaled nitric oxide, can be assessed during clinic visits, the past values of these measures are often not taken into account or at least assessed in a limited manner. From clinical experience, the general practitioner knows the history of his or her patient and judges the stability of the patient's asthma and exacerbation risk based on past events[5,9-13]; a complex disease such as asthma follows a dynamic course that relates to both past and current patient status. It is therefore proposed that any concept of asthma control needs to incorporate an assessment of individual patient history, as well as future potential for experiencing poor asthma outcomes.[1] Although assessing asthma control at a single point in time is of some value, multiple measurements of lung function, symptoms, or β_2-agonist use over time are required to adequately determine asthma control and to more reliably predict future response in clinical trials.[14]

Home monitoring of peak expiratory flow (PEF) offers one avenue to obtain multiple observations over time, but studies of PEF variability in the past have yet to produce a clear and clinically relevant parameter that can quantify past history or assess risk of exacerbation.[15,16] We have previously developed a method that uses daily fluctuations in PEF to calculate conditional probabilities (π) of a future decrease or sudden deterioration in lung function[17,18] given a patient's current lung function. The daily fluctuations in PEF exhibit fractal-type long-range correlation properties, which implies that there are deterministic components in daily lung function variability that can be used to predict future behavior in a probabilistic manner.[18] However, these predictions were calculated for treatment groups rather than for individual patients. There is thus far no statistical method that can estimate the risk of exacerbations for individual patients because most risk-assessment strategies have been based on population statistics (eg, increased risk of smokers in comparison with nonsmokers). Medicine is moving toward individualized phenotyping, risk assessment, and treatment strategies, and there is an urgent need for better statistical prediction methods for individual risks.

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Abbreviations used
ICP: Individual conditional probabilities
PEF: Peak expiratory flow
%predFEV$_1$: Percent predicted FEV$_1$
%predPEF: Percent predicted peak expiratory flow
π: Conditional probabilities
ROC: Receiver operating characteristic

In this study we introduce and validate a novel method of calculating individual conditional probabilities (ICP) to determine future risk of exacerbation in asthmatic patients using data from 2 past studies in which lung function was monitored electronically.[19,20]

METHODS

The following represents a summarized version of the methodology. Detailed methods can be found in this article's Online Repository at www.jacionline.org.

Original datasets

In study A[19] 309 adult patients with asthma for 3 or more years and uncontrolled severe asthma for 1 or more years[21,22] were randomized to receive placebo or different doses of a trial drug for 52 weeks. From weeks 0 to 24, a constant dosage of inhaled corticosteroids with or without oral corticosteroids was maintained. From weeks 24 to 52, downtitration of corticosteroid treatment was attempted. For the present study, twice-daily electronically recorded PEF data (Jaeger AM2+; VIASYS Healthcare, Hoechberg, Germany) from weeks 0 to 52 of the trial were used from patients in the placebo group who had completed 24 or more weeks and had entered the downtitration phase (n = 77).

In study B[20] 61 adult patients with poorly controlled asthma[23] were randomized to receive 8 weeks of either 1600 μg/d or 3200 μg/d budesonide treatment, followed by 8 weeks of 1600 μg/d and 14 months of downtitration. For the present study, twice-daily electronically recorded PEF data (MicroMedical DiaryCard, Rochester, United Kingdom) from weeks 0 to 72 of the trial were used from all patients who had completed 16 or more weeks (n = 58).

Details of both studies have been published previously,[19,20] and they were approved by the relevant ethics committees.

Calculation of conditional probabilities

Briefly, of the original time series (Fig 1, *A*), the first 64 days of PEF data served as a reference observation period (Fig 1, *B*) for each patient. A PEF quality control criterion was used whereby patients with 10% or more data missing from the completed monitoring period were excluded from the main analyses. Fluctuation analysis was performed as previously described[18,24] to obtain the time correlation properties of PEF from this period. The distribution properties of PEF (mean, SD, and skewness) were also calculated. Both properties were subsequently used to simulate a new time series of 5,000 PEF data points for each patient with the same correlation and distribution properties as the original data (Fig 1, *C*). This was done as previously described[17,18] but based on data from each patient.

Next the simulated data were used to calculate π values; given an initial percent predicted PEF (%predPEF), the π value was defined as the probability of encountering a decrease in PEF to less than a set threshold of 80% on 2 consecutive days within 30 days calculated over multiple overlapping windows moved progressively over the simulated data.[18] The end point of this procedure is a reference curve (Fig 1, *D*) relating π values to initial %predPEF for each patient, which predicts the probability of a lung function decrease within 30 days as a function of the initial %predPEF on the first day of that period.

Calculation of actual events of PEF decrease

A testing window of 30 days after the 64-day observation period in the original PEF data was used to validate the predictive ability of the calculated π values (Fig 2, *A*). Here the initial %predPEF was determined, and the corresponding π value was obtained from the reference curve previously calculated for that patient (Fig 2, *B*). This π value was then compared with the number and occurrence of actual events of decrease in %predPEF to less than the threshold within the future testing window (Fig 2, *C*).

The above calculations were repeated for multiple pairs of observation periods and testing windows within the entire study period used for analysis (Fig 2, *D*). Thus we could determine the relationship of actual events of a decrease in %predPEF versus π values averaged over all windows for each patient (Fig 2, *E*).

Determination of clinically defined exacerbations

The π values were also compared with occurrences of actual exacerbations defined clinically as per the original studies (Table I) as outcome. Because the numbers of events, clinically defined exacerbations, or both were low for some patients, when looking at occurrences of outcome, the observation period and testing window were moved progressively in an overlapping manner to increase the number of observation periods relevant to an event or exacerbation. This would be analogous to a patient's lung function history being continually updated to renew his or her assessment of risk.

Statistical analysis

Associations between π values and actual future numbers of PEF events (count outcome) were made by examining the adjusted R^2 value in a nonlinear regression between the π value and the number of PEF events averaged for each patient.

Associations between π values and occurrence of PEF events (binary outcome) were examined by using logistic regression. Because of the use of overlapping windows, the effect of adjusting for clustering at the patient level was examined, whereby robust SEs in the regression were recalculated, allowing for correlation of multiple observations within the same patient. In addition, receiver operating characteristic (ROC) curves were used to compare the predictive ability of π values with that of the closest available clinic-recorded prebronchodilator FEV$_1$ measurement before each analysis window expressed as a percentage of predicted value (percent predicted FEV$_1$ [%predFEV$_1$]). The direction of %predFEV$_1$ was reversed to be consistent with the expected direction of a higher π value (higher risk).

Associations between π values and the occurrence of clinically defined exacerbations (binary outcome) were examined in a similar manner as for the PEF events above.

In all analyses the standard period in which PEF events were counted and the testing window used was 30 days (ie, 60 data points) because this window size has been shown to yield stable π for most patients (see this article's Fig E1 in the Online Repository at www.jacionline.org), and a threshold of a decrease to less than 80% of predicted PEF was used to determine the occurrence of a PEF event. We also examined the effect of using a shorter testing window size of 15 days (ie, 30 data points) and of using a lower threshold at 60% of predicted PEF.

All statistical analyses were performed with Intercooled Stata version 11 software (StataCorp, College Station, Tex).

RESULTS

Subjects' demographics and baseline characteristics can be found in Table II. In summary, 35 of 78 patients in study A (with severe persistent asthma uncontrolled by high-dose inhaled [± oral] corticosteroid and long-acting β_2-agonist treatment) and 34 of 61 patients in study B (with uncontrolled asthma and not necessarily taking any inhaled corticosteroids at entry [maximum dose, 1200 μg/d]) had sufficient data for analysis satisfying the quality control criterion.

The mean ± SD number of exacerbations per patient was 3.1 ± 3.0 for the first 24 weeks of study A and 0.9 ± 1.2 for the first 16