

Predicting asthma exacerbations: Peak expiratory flow revisited

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The ability to predict and prevent future exacerbations has been a consistent focus of asthma research. Although some progress has been made on identifying factors associated with an increased risk of exacerbation at the population¹⁻³ and individual⁴ levels, no measure or instrument is available for widespread use in the asthma community.

In this issue of the *Journal*, Thamrin et al⁵ present a statistical method used to calculate the future exacerbation risk for a patient (as defined by deterioration in percent predicted peak expiratory flow [PEF]) based on the history of fluctuations in lung function (percent predicted PEF). The authors challenge us to reframe our analytic approach to asthma. Frey et al⁶ have suggested that a patient with asthma should be thought of as a complex, nonlinear dynamic systems network; such a network exhibits fluctuations over time in physiologic and clinical variables. However, such a system also exhibits memory effects, and although changes can occur over time, the recent past will include most of the pertinent information needed to predict the short-term future risk.

Viewing asthma through this framework, it follows that the single best individual parameter to predict the risk of an exacerbation over the next year is the history of an exacerbation in the prior year.⁷ The natural history of asthma in any given patient is a summation of personal characteristics (eg, demographics, inflammatory profile, and lung mechanics), genetics, both the physical (exposure to environment [environmental tobacco smoke, pollution, and allergens]) and psychosocial (access to care) environment, and therapy (including adherence). The complex interaction of these factors results in the overall clinical phenotype expressed by a patient, and this helps explain why the recent past is a strong predictor of future events. Modeling asthma as a complex, nonlinear dynamic system also fits with our increasing recognition of the heterogeneity of asthma. Patients with asthma present differently in regard to symptoms, physiologic measures, inflammatory indices, and perception of obstruction; measuring a single parameter at a single point might not fully categorize future risk, but analyzing the fluctuations in a measure over time might improve our ability to predict future events.

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Using this framework at a population level, Frey et al⁶ published on the use of daily fluctuations in PEF to calculate conditional probabilities of a future deterioration in lung function (PEF) based on the current level of lung function (PEF). In the current article Thamrin et al⁵ extend this prior analysis and apply the analytic framework to the individual patient. The authors illustrate how 2 properties of the variation of daily PEF values, the time correlation and distribution of PEF values, can be used to predict future behavior. Using these 2 properties, the authors then simulate a new time series of percentage of PEF for each person, increasing the number of data points available to calculate the probability of encountering an exacerbation (π).

For this analysis, the authors define an exacerbation as a decrease in PEF to less than 80% of predicted value on 2 consecutive days within a 30-day period. In prior studies poor associations have been observed between PEF criteria for an exacerbation and a clinician's prescription of corticosteroids.^{8,9} Using diary card data from the Pediatric Asthma Controller Trial, Covar et al⁷ assessed the predictive value for an imminent exacerbation (defined by initiation of corticosteroid or emergency department visit) by using diary card tracking of PEF reduction, symptoms, or rescue albuterol use. The positive and negative predictive values for all 3 measures were low. However, Covar et al assessed a single value for each measure (ie, 3 days, 2 days, the day before, and the day of initiation of corticosteroid or emergency department visit), whereas Thamrin et al⁵ used the time correlation and distribution of PEF values over a 2-month period to predict future behavior. Of note, Thamrin et al did validate the calculated values of π for each subject with the clinical exacerbation events observed in the trial. Although a decreased ability to predict clinically defined exacerbations compared with predicting decreases in PEF was observed, the predictive ability for clinical exacerbations was comparable with that for other existing measures.

To improve power, the authors use overlapping windows to make use of all possible observation periods preceding the available events; this likely enhances the relationship between the estimate of risk and actual events. In addition, the authors use simulation to increase the number of data points and improve the estimation of the conditional probability for each person. Both techniques increase the complexity of applying this analytic method in clinical practice, yet the use of overlapping time windows does reflect how the method would be applied in real life. Similarly, the technique is based on a rolling assessment period; this allows changes in underlying disease over time to be incorporated into the conditional probability generated for a patient. One could envision a risk calculation that is updated and fed back to the patient on a daily basis, potentially improving self-management.

The authors combined subjects from 2 randomized controlled trial populations examining persons with either severe persistent

asthma or uncontrolled asthma.^{10,11} It is possible that the fluctuation patterns of PEF are related to asthma control, asthma severity, or both. A much longer observation period would be needed to examine whether this analytic technique could be applied in patients with milder asthma in whom exacerbations are much less frequent events. Of note, the authors did examine both the Global Initiative for Asthma category and inhaled corticosteroid dose at the end of the study and found neither had a significant effect in the relationship between π and PEF events when added to the regression model.

The ability of Thamrin et al⁵ to extend this technique from the population level to the individual patient is an important step forward. However, 2 questions remain: (1) What does this add to our existing ability to predict future exacerbations? (2) What are the logistics of taking this into clinical practice and being able to assess the conditional probability at the individual level in real time? Forno et al⁴ recently published a clinical decision score that used information easily obtained in the outpatient ambulatory setting. In their analysis the clinical score, when used in the validation set, demonstrated an area under the curve of 0.75, which is very similar to the area under the curve for study B in the current analysis. Therefore it is important to ask what the collection of serial PEF data and their associated analysis (which is not trivial even if software could be developed that was easy to use in association with an electronic PEF monitor) will add to parameters that are easily obtained at a single visit. Although the approach presented by Thamrin et al⁵ can predict the risk of exacerbation within the following month or possibly shorter periods, to realize the benefit from this technique, we need to rely on patients to reliably perform twice-daily PEF measurements. The use of electronic PEF diaries compared with paper diaries has improved greatly the reliability of the data we obtain,^{12,13} but we are still limited by our patient's ability to record that data for us on a regular basis.^{14,15}

The real value of the analysis presented by Thamrin et al⁵ might be the use of serial measurement and not specifics of PEF compared with other measures of lung function (FEV₁ or potentially FEV₁/forced vital capacity) or asthma status (rescue β -agonist use or biomarkers). Asthma is a heterogeneous condition, which varies both between patients and within a given patient over time; the ability to use this analytic framework to examine a given measure or set of measures serially over time might improve

our prediction of future risk. In addition, the current analysis outlines a risk value, which can theoretically be updated on a daily basis in a home setting by using telemonitoring.

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