Airway inflammation in asthma : from concept to the clinic

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Chapter
6

Asthma guidelines: towards evidence-based application of peak flow

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Abstract

Background: In the current GINA guidelines, the assessment of asthma control is based on symptoms and lung function. We investigated the value of including PEF-variability in addition to symptoms and $ß_2$-agonist use, in predicting the development of poor asthma control in a prospective study.
Methods: 75 patients with asthma had GINA step determined and treatment adjusted at baseline and after 3 months of follow-up. Data were analysed to ascertain the extent to which each clinical feature was involved as decisive factors in determining the GINA grade. Logistic regression analysis was applied to determine the value of PEF-variability in predicting asthma control at the second visit in the whole group and in a sub-group of patients with GINA grade 1 and 2 at entry. The optimal cut-off value for loss of control was determined by the receiver operating characteristic (ROC) curve.
Results: A PEF-variability of ≥20% determined in 0% of cases the GINA step at baseline. However, as a continuous variable, PEF-variability provided additional information on top of symptoms and $ß_2$-agonist use in predicting loss of control (total group: OR=1.14; p=0.003 and sub-group: OR=1.37; p=0.012). Patients in GINA step 1-2 with PEF-variability >10% at visit one had a RR of 7.7 (p=0.034) for an increase towards GINA step 3-4 at follow-up as compared to patients with PEF-variability ≤10%.
Conclusions: PEF-variability provides useful information in addition to symptoms and $ß_2$-agonist use and may therefore be valuable to adjust therapy in order to prevent loss of asthma control.

Introduction

The current Global Initiative for Asthma (GINA) guidelines for the treatment of asthma recommend the assessment of symptoms and lung function for successful management of asthma (1). Since their first publication in 1993, the GINA guidelines have taken a stepwise standardized approach to asthma treatment, with the treatment level based on four grades or steps which are determined by clinical features such as daytime and night-time symptoms and PEF-variability (Figure 1A). The presence of one of the features of a GINA step is sufficient to place a patient in that category; thus, the GINA step is determined by the worst among the patient's clinical features. The cut-off values between the GINA steps are not evidence-based, but are derived from presumed clinical significance as assessed by an expert panel through consensus (1). In the 2002 GINA guidelines, a separate table was added for ongoing assessment of control *during* treatment. This table (Figure 1B) utilised a similar categorisation of symptoms and lung function, in combination with the "Treatment Step" of daily medication. The clinical

Figure 1A

Figure 5-6. Classification of Asthma Severity by Clinical Features Before Treatment

STEP 1: Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month ● FEV1 or PEF ≥80% predicted ● PEF or FEV1 variability <20%
STEP 2: Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month ● FEV1 of PEF ≥80% predicted ● PEF or FEV1 variability 20-30%
STEP 3: Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting ß2-agonist ● FEV1 or PEF 60-80% predicted ● PEF or FEV1 variability >30%
STEP 4: Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities ● FEV1 or PEF ≤60% predicted ● PEF or FEV1 variability >30%

Figure 1B

Figure 5-7. Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment

	Current Treatment Step		
	Step 1: Intermittent	Step 2: Mild Persistent	Step 3: Moderate Persistent
Patients Symptoms and Lung Function on Current Therapy	Level of Severity		
Step 1: Intermittent			
Symptoms less than once a week		Mild	Moderate
Brief exacerbations	Intermittent		
Nocturnal symptoms not more than twice a month		Persistent	Persistent
Normal lung function between episodes			
Step 2: Mild Persistent			
Symptoms more than once a week but less than once a day	Mild	Moderate	Severe
Nocturnal symptoms more than twice a month but less than once a week	Persistent	Persistent	Persistent
Normal lug function between episodes			
Step 3: Moderate Persistent			
Exacerbations may affect activity and sleep			
Nocturnal symptoms at least once a week	Moderate	Several	Severe
60% < FEV1 < 80% predicted OR	Persistent	Persistent	Persistent
60% < PEF < 80% personal best			
Symptoms daily			
Step 4: Several Persistent			
Symptoms daily			
Frequent exacerbations	Severe	Severe	Severe
Frequent nocturnal asthma symptoms	Persistent	Persistent	Persistent
FEV1 ≤60% predicted OR			
PEF ≤60% of personal best			

Figure 1. Classification of asthma severity in GINA guidelines (A) before treatment and (B) during treatment (1).

features were now considered to reflect the level of control which had been achieved with treatment (1;2). It can be seen from this approach that the underlying asthma severity is perceived as driving the appropriate maintenance treatment in order to achieve control of asthma. Indeed, a prospective evaluation showed that acute health care utilisation was predicted by an index of asthma control (3).

There is some controversy over whether the assessment of asthma control should include PEF measurements, at least partly because of difficulty in achieving good adherence with monitoring. In clinical practice guidelines, the rationale for including both symptoms and lung function in the classification of asthma control in individual patients has been

that both symptoms and airway obstruction are integral to the definition of asthma, and there is a wide variation in the way individual patients manifest inadequacy of asthma control (4). Monitoring of peak expiratory flow (PEF) has been recommended to overcome poor perception or under-reporting of symptoms by patients. Furthermore, it has been found that successful control of both symptoms and peak expiratory flow (PEF) leads to improvements in quality of life which therefore benefits the patient (5).
Peak flow measurements may be summarised in several different ways, including the PEF-level (clinic PEF measured by the clinician, or, alternatively, mean daily PEF, expressed as a percentage of predicted or of personal best) and PEF-variability (amplitude as percentage of mean value). In the 2002 GINA guidelines, there is an unexplained distinction between the initial assessment, when both PEF-variability and PEF-level are used (Figure 1A), and the ongoing assessment during treatment, when PEF-level alone is used (Figure 1B) (1).
To date, there are few data on the relative contribution of symptoms and PEF to the classification of asthma control and the resulting maintenance treatment according to GINA guidelines in clinical practice. We assessed the extent to which different levels of PEF-variability provide information on asthma control in addition to that provided by symptoms and $ß_2$-agonist use. Furthermore, we evaluated the value of including PEF-variability in addition to symptoms and $ß_2$-agonist use in predicting the development of poor asthma control in a prospective study.

Methods

Subjects

Seventy-five atopic patients with mild to moderate persistent asthma, who participated in the 2-years prospective AMPUL (Asthma Management Project University Leiden) study, were included in the analysis (6). All patients had a history of episodic chest tightness or wheezing and prior to entry were treated with or without inhaled steroids. They were 18-50 years and non- or ex-smokers (>1 yr; <5 packyrs). The pre-bronchodilator forced expiratory volume in one second (FEV_1) was more than 50% of predicted, whilst post-bronchodilator FEV_1 was within the normal range (>80% predicted). All were hyperresponsive to methacholine (PC_{20} < 8 mg/ml) (6).
The medical ethics committee of the Leiden University Medical Center approved the study and all participants gave written informed consent.

Design

In the prospective study, treatment was adjusted every 3 months for 2 years in a referral hospital according to the GINA guidelines. Full details of the methodology have previously been published (6). For the present analysis, the first 2 visits (i.e. baseline visit, at which the first treatment adjustment was made, and the first follow-up visit, 3 months later) were used.
Before each visit, patients kept a diary card for 2 weeks on which day- and night-time symptoms, use of ß2-agonists and AM and PM PEF were recorded. Symptoms were

recorded twice daily on a 0-4 scale (6), and the scores were converted to a categorical scale equivalent to that in the GINA guidelines. AM and PM peak flows were used to calculate PEF-variability (amplitude%mean) (1), using the PEF cutpoints specified in the GINA guidelines (7). As recommended in the guidelines, the worst feature was used to determine the GINA step and hence the level of treatment for the first 3 months. Twenty-three patients had newly detected asthma and were classified according to Figure 1A of the guidelines, whilst the other 52 patients were on regular inhaled steroids and were therefore classified according to Figure 1B.

Analysis

We analysed data from the first visit to ascertain the extent to which each clinical feature was involved as (one of) the decisive factors in determining the GINA grade. The clinical features which are accessible to a general practitioner (day and night-time symptoms, bronchodilator use and PEF variability) were included in the analysis. Second, logistic regression analysis was applied to determine the value of PEF-variability as a continuous variable, in addition to symptoms, in predicting asthma control at the second visit (dependent variable: GINA grade 1 and 2 *versus* GINA grade 3 and 4 at visit two; independent variables: GINA grade and PEF variability at visit one). A sub-group analysis was performed for the patients in GINA grade 1 and 2 at visit one. Only these patients might be classified in a higher GINA grade based on their PEF-variability, whereas for the patients in GINA grade 3 and 4, adding PEF variability could not change their classification, since symptoms and or bronchodilator use had already placed them in a higher GINA grade. Next, based on a receiver operating characteristic (ROC) curve, an optimal cut-off value for PEF variability was selected for prediction of loss of control (GINA step 1 and 2 versus GINA step 3 and 4) at the second visit. Finally, logistic regression analysis was carried out to determine the risk of patients in GINA grade 1 and 2 with a PEF-variability higher than the selected cut-off value to be classified in GINA grade 3 or 4 at the second visit.
P-values of less than 0.05 were considered as significant and STATA was used to analyse the data.

Results

Contribution of clinical features to GINA grade

At Visit 1, the distribution of patients among the GINA steps was Step 1 17%, Step 2 28%, Step 3 35% and Step 4 20%. The GINA grade was determined by one single factor in 82.1% of the patients. Figure 2 shows the percentage of patients in whom a particular clinical feature was involved as (one of) the determining feature(s) to allocate an individual patient to GINA step 2 or higher. Symptom was by far the most dominant feature in determining the GINA level and thereby the level of asthma treatment (figure 2, top panel). For no patient (0%) was the level of control determined by PEF-variability, using the cut-off value of 20% which is specified in the GINA guidelines.

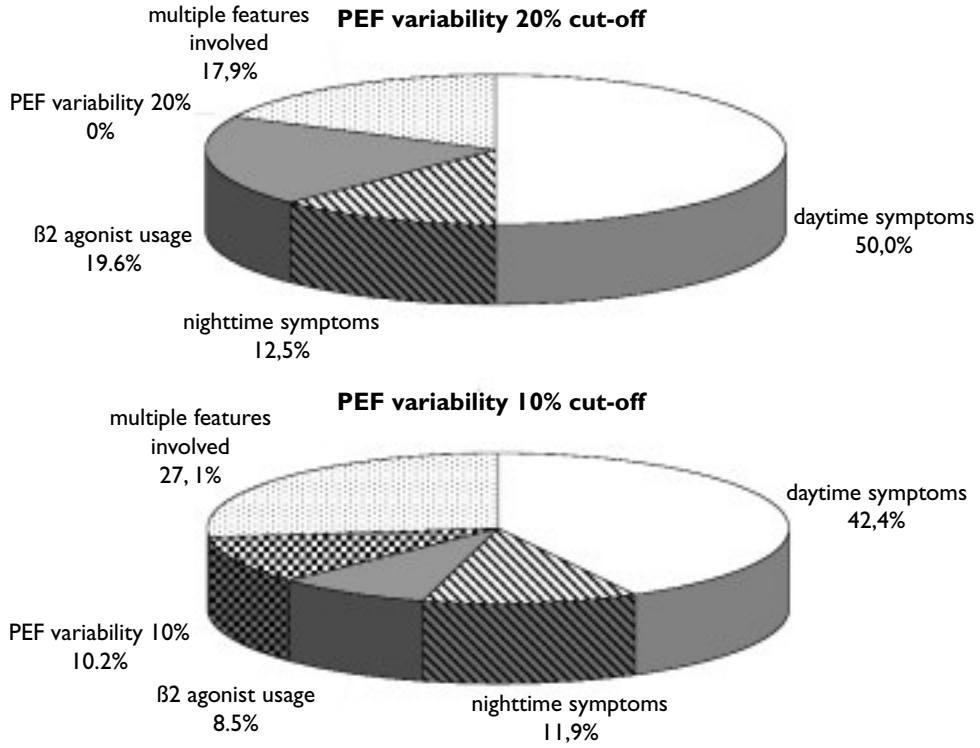

Figure 2. Percentage of visits on which a particular clinical feature was involved as (one of) the driving features to allocate a patient in GINA severity grade 2 or higher. Two different cut-off value for PEF-variability were used in the analysis: when using PEF-variability < 20% (top panel) and when using PEF-variability < 10% (bottom panel).

Prognostic value of PEF-variability

Logistic regression analysis showed that at the first visit, PEF-variability significantly provided additive information on top of symptoms in predicting the level of asthma control (GINA grade 1 and 2 *versus* GINA grade 3 and 4) at the second visit (RR=1.14; p=0.003).

Sub-group analysis

A logistic regression, analysing the additional value of PEF-variability in determining asthma control, was repeated in the sub-group of 40 patients categorised in grade 1 and 2 at the first visit. In this sub-group, again PEF-variability on top of symptoms significantly predicted asthma control at the second visit (RR=1.37; p=0.012).
The area under the curve (AUC) of the ROC curve for using PEF-variability on top of the current guidelines for predicting asthma control at the second visit was 0.75. From this ROC curve (Figure 3) a cut-off value of PEF-variability >10% was selected based on the high specificity and likelihood ratio.

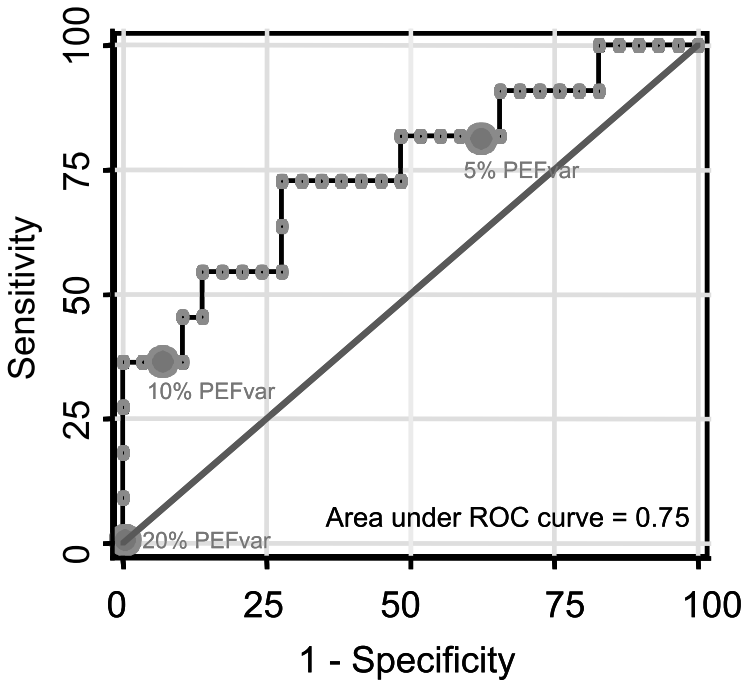

Figure 3. ROC curve for using PEF-variability on top of the current guidelines for predicting asthma severity (GINA grade 1 and 2 versus GINA grade 3 and 4) at the second visit. The area under the curve was 0.75.

Applying cut-off value of PEF-variability >10%

The cut-off value of PEF variability 10% gave a sensitivity of 36%, a specificity of 93% and a likelihood ratio (LR) for a positive result of 5.27.

Logistic regression analysis showed that patients in GINA control step 1 or 2 with PEF variability >10% at baseline had an OR of 7.71 (p=0.034) for an increase in GINA level at the second visit as compared to patients with PEF variability ≤10%.

A retrospective re-classification of GINA categorisation at baseline was performed using PEF-variability with the proposed cut-off value of >10%, instead of the existing cutpoint of ≥20%. With this cutpoint, PEF-variability would have determined the GINA step at baseline in 10.2% of the patients [figure 2, bottom panel].

Discussion

Our results have shown that PEF variability provides information about asthma control in addition to symptoms and $ß_2$-agonist use. Furthermore, this study demonstrated that patients who were classified as being in GINA step 1 and 2 using the existing GINA criteria, but who had PEF-variability >10% had an almost 8 times higher risk for loss of asthma control 3 months later compared to patients whose PEF-variability was ≤10% at baseline. This suggests that including PEF-variability in the assessment of asthma control during treatment can improve the current guidelines for the treatment of asthma, but that the existing cut-points for PEF-variability are too high.

This is the first study showing the additional value of measuring PEF-variability in the management of asthma. These results extend previous findings which showed that PEF-variability in selected populations is valuable for epidemiological and diagnostic purposes (8-10). We have demonstrated that when using a cut-off value of 10%, PEF-variability is able to identify patients with an increased risk of loss of control of asthma. Previous studies have shown that patients with poor asthma control demonstrate higher PEF-variability compared to stable asthmatics (11). Furthermore, our findings are consistent with results from Nathan *et al.* who showed that a 10% cut-off value for PEF variability identifies patients with greater benefit from treatment (12).

We believe that our results have not been affected by patient selection or the methods of asthma monitoring. The current group of asthmatics seems to be representative of a broad range of asthma severity, since our patients were equally distributed over the 4 GINA grades. We cannot exclude that a patient group with a different balance of asthma severity would lead to different results. However, all our measurements were strictly based on asthma guidelines, allowing extrapolation of our findings to asthma care elsewhere.

The 10% cut-off value of PEF-variability was selected based on the high specificity and likelihood ratio observed. Even though we have shown that this cutpoint identifies patients at greater risk of loss of control, the most optimal cut-off value has to be investigated in large follow-up studies.
The cut-off value of PEF variability of 10% is in contrast with the 20% cut-off used in the current GINA guidelines. The number of PEF readings per day could readily explain this lower value. Indeed, reducing the frequency of measurements has been shown to underestimate the diurnal variation in PEF (13,14). The cut-off value of 20% stated in the present guidelines was based on studies where PEF was determined more frequently (18), whereas when PEF was measured twice daily, as is current practice, the upper 95% confidence limit for normal PEF-variability was 8-9% (15;16). Indeed in our study, in which PEF was measured twice daily, the PEF-variability was below the conventional cut-off value of 20% in almost all patients and therefore never determined the level of treatment, although these patients by other criteria had sub-optimally controlled asthma.

How can these results be interpreted? Airway hyperresponsiveness is an important characteristic of asthma (1). Previously, we have shown that asthma treatment aimed at reducing airway hyperresponsiveness is more effective in gaining control than therapy adjustment based on symptoms and level of lung function alone (6). Diurnal changes in PEF have been suggested as an indicator of the responsiveness observed in asthma (17). In this respect, the additional value of PEF-variability in asthma management observed in our study is not surprising. In addition, PEF-variability appears to be associated with eosinophilic inflammation in sputum in patients with asthma (18). Again, a strategy that minimises eosinophilic inflammation leads to improved asthma management as compared with a standard strategy (19). This implies that a feature reflecting airway hyperresponsiveness and/or airway inflammation should be included in the guidelines

of asthma management to optimise control of the disease. PEF-variability might be an appropriate indirect marker for this, which is accessible even in primary care settings where bronchial provocation testing or sputum induction are not readily available.

In conclusion, PEF-variability with a cut-off level of 10% provides additional information to monitor asthma control in addition to symptoms and lung function. Our data suggest that determining PEF-variability is not only useful for the diagnosis of asthma, but is also valuable for adjusting therapy of patients during treatment to thereby prevent loss of asthma control. These findings imply that the current cut-off values of PEF-variability should be revisited.

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