Early detection of asthma exacerbations by using action points in self-management plans

Persijn J Honkoop, MD\textsuperscript{1,2}, D. Robin Taylor\textsuperscript{3}, Andrew D. Smith, MD\textsuperscript{3}, Jiska B Snoeck-Stroband, MD\textsuperscript{1}, Jacob K Sont\textsuperscript{1}

\textsuperscript{1} Dept of Medical Decision Making, Leiden University Medical Center, Leiden, The Netherlands
\textsuperscript{2} Dept of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
\textsuperscript{3} Dept of Respiratory Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Correspondence to:
P.J.Honkoop, MD
Leiden University Medical Center
Postzone J-10-s, room J-10-87
Albinusdreef 2
PO Box 9600, 2300 RC Leiden
T +31 (0)71 526 4904
F +31 (0)71 526 6838
M: P.J.Honkoop@lumc.nl
ABSTRACT

Objective
Our aim was to validate optimal action points in written action plans for early detection of asthma exacerbations.

Methods
We analysed daily symptoms and morning peak-flows (PEF) from two previous studies. Potential action points were based on analysis of symptom scores (SDs) percentage of personal best PEF, or PEF variability in relation to a run-in period, or combinations of these measures. Sensitivity and specificity for predicting exacerbations were obtained for each action point. The numbers needed to treat to prevent one exacerbation and the time interval between reaching action point criteria and the start of the exacerbation were calculated. Based on these parameters, the optimal action points for symptoms, PEF, and PEF plus symptoms were determined, and their performance compared to published guidelines action points.

Results
The optimal action points were: for symptoms, statistical variability (SDs); for PEF, <70% of personal best. The combination of PEF plus symptoms performed best, with improved specificity and earlier detection. The main benefits associated with using these action points was to reduce false positive rates for detecting exacerbations.

Conclusion
Early detection of asthma exacerbations can be improved using a composite action point comprising symptoms and PEF measurements over one week.
BACKGROUND

Exacerbations of asthma are common and even when asthma is mild, constitute a significant health risk [1]. Assessing future risk of adverse events, including exacerbations, and educating patients to use a self-management plan is recommended [2-6].

Self-management includes developing individualised Written Asthma Action Plans (WAAP). WAAPs specify the level of symptoms or peak expiratory flow (PEF) (called action points, APs) at which to adjust medication (usually starting oral corticosteroids) in order to prevent or reduce the severity of exacerbations. To ensure effective intervention an AP should detect an imminent exacerbation well before its onset.

Gibson et al. have previously validated several APs using quality control analysis (QCA) [7,8]. However, in the Global Initiative for Asthma (GINA) guidelines and the Dutch national guidelines, thresholds for symptoms or PEF are not specified [3, 9]. Although APs in the current British Thoracic Society (BTS) and National Heart Lung and Blood Institute (NHLBI) guidelines are more specific, these APs have not been validated [2, 5, 6]. The optimum time point that changes in symptoms or PEF may be detected, or the relevant thresholds reached prior to an exacerbation are largely unknown. This lack of validation means that physicians often determine APs for individual patients empirically. If APs are inaccurately selected, this potentially leads to over treatment (false-positive APs) or missed opportunities for early intervention (false-negatives).

In this study, our aim was to develop optimal action points, based on symptoms and/or PEF threshold levels for early detection of asthma exacerbations which allow timely
intervention in patients with mild-moderate asthma. Subsequently we aimed to validate the
performance of the optimised APs in a similar but separate study population. **METHODS**

We analysed asthma symptoms, morning PEFs, the occurrence of exacerbations and
the use of prednisone using data from written daily diaries from two previous studies [10, 11]. The development dataset was obtained from a randomized controlled trial designed to
compare the effects of 6 months treatment with regular inhaled salbutamol, salmeterol or
placebo [10] The validation dataset was obtained from a single-blind placebo-controlled trial
which explored the use of exhaled nitric oxide (FENO) to guide treatment in chronic asthma
[11]. The follow-up was one year.

**Subjects**

There were 165 patients in the development dataset and 94 in the validation dataset,
all with stable mild to moderate chronic asthma [10, 11].

**Daily diaries**

In both studies, daily diary recordings included: symptoms of daytime and night-time
chest tightness/wheeze/dyspnoea, cough, sputum production, exercise impairment, and
appearance or increased frequency of nocturnal awakening. All were scored on a 0-3 scale or
by a yes/no response where appropriate. The best of three PEF measurements was also
recorded each morning and evening. Missing data were interpolated, using the mean of
recordings from the previous and following day.

**Exacerbations**

Exacerbations were defined in both studies using a composite daily asthma score. The
scoring criteria were similar between the two studies, but differed regarding the use of beta-
agonist “reliever” and nocturnal awakening (see Table 1, Taylor et al., and Table 2, Smith et al [10,11]). In brief, major exacerbations were defined as either a visit to the emergency department; or PEF lower than 40% personal best (pb) for ≥1 day; or PEF <60% pb ≥2 days plus an increase in symptoms; or PEF <60% pb for ≥1 day and PEF <75% pb ≥2 days with an increase in symptoms.

During the study, courses of prednisone were administered in response to deteriorating symptoms and/or peak flows, or at the discretion of patients or clinicians independently of diary data. Prednisone use for ≥3 days is widely used as a definition for exacerbations [4]. Therefore, as a sensitivity analysis, we also assessed the predictive utility of APs using this alternative definition.

**Action Points**

A range of pre-specified APs was evaluated. For symptoms, we assessed APs used in currently recommended WAAPs: the occurrence of nocturnal awakening, or the appearance of any symptoms [2, 3, 6, 9]. Additionally, we evaluated APs based on QCA of symptoms using standard deviations (SDs) from the mean symptom score during run-in for each patient. To this end we developed a composite daily symptom score (range 0-6), which combined all daily recorded individual symptoms and “reliever” beta-agonist use; with higher scores representing more severe symptoms (see Table 5, online supplement). The mean score and its SD were determined per patient during the run-in period when asthma was well controlled. Subsequently, occasions characterised by deviation from the mean by more than 1, 2 or 3 SDs were evaluated as potential APs. In patients without any symptoms during the run-in, the mean symptom score and SD was 0. In these cases the 1, 2 and 3 SD thresholds were set at 0.17, 0.34 and 0.50 respectively, representing the minimal possible changes in composite symptom score.
For PEF, the APs were derived from percentages of personal best morning PEF measurement obtained during the run-in period (% pb), or QCA based on the approach outlined by Gibson, [7, 8]. We also analysed whether combining PEF and symptoms as a composite AP might perform better, since using single outliers of PEF or symptoms alone might result in relatively high false positive rates for exacerbation prediction. Therefore, we assessed whether a combination of symptom and PEF thresholds were reached on the same day, and also within a one week time window. Finally, we assessed the performance of the APs currently recommended by the National Heart Lung and Blood Institute (NHLBI) which are based on both symptoms and PEF (“yellow zone”, Figure 3-10A, page 117 [2]). Since it is not clear whether reaching the threshold for either symptoms or PEF alone is sufficient or both are required, we analysed both options.

For each patient, every week in the diary recordings was coded as either 'stable week' when no exacerbation occurred, or ‘pre-exacerbation week’ for the week prior to an exacerbation. For all stable and pre-exacerbation weeks, we assessed whether the AP(s) either predicted a future exacerbation (when one or more of the daily recordings in that week fulfilled criteria for that specified AP), or predicted that a future exacerbation would not occur (when daily recording(s) did not reach the defined thresholds) (see Figure 1).

**Analysis**

All analyses were performed with STATA version 11, StataCorp LP. Contingency tables for each AP threshold were constructed to calculate performance characteristics including sensitivity, specificity, accuracy and area under the receiver operating characteristic (AUC) curve for predicting an exacerbation. In addition, for each AP threshold we assessed the (potential) Number Needed to Treat (NNT) in order to prevent one exacerbation, given a
hypothetical perfect treatment, and Early Detection, defined as the number of days before the onset of an exacerbation the AP was reached for the first time in a pre-exacerbation week. NNT was calculated by dividing the total number of times an AP was reached (true positives and false positives) by the number of times it accurately predicted a future exacerbation (true positives).

The APs which performed optimally were determined within four categories: symptoms solely; PEF solely; symptoms and PEF on the same day; and symptoms and PEF within one week prior to an exacerbation, using the development dataset. Optimal performance was defined as a sensitivity of at least 75% combined with the best trade-off between Early Detection and (potential) NNT. To determine this outcome, we plotted the number of days an exacerbation was predicted before its occurrence against the NNT, for a series of different APs (see Figure 2).

To assess the external validity of the optimal APs derived from the development dataset, their performance was assessed and compared to several published APs using the validation dataset [11].
RESULTS

The development dataset consisted of daily recordings from 164 patients. Eighty-eight exacerbations, defined using diary data, occurred during 18 months of follow-up. Exacerbations occurred in 39 different patients, mean rate 1.8 /patient/year, ranging from 1 to 13. 147 exacerbations, defined as the use of a course of oral prednisone, occurred during the follow-up interval.

In the validation dataset 94 patients provided daily recordings. Twenty-two exacerbations occurred. Exacerbations occurred in 17 patients, and the mean rate was 1.5 /patient/year range 1 to 5. Oral prednisone was used on 75 occasions.

The characteristics of patients from both studies are listed in Table 1.
**Action points**

The performance of 25 potential APs was analysed (a complete overview of results is presented in the online supplement, Tables 4a-d). Six APs were based on symptoms, 8 on PEF, 9 on combinations of symptoms and PEF on the same day, and 2 on combinations of symptoms and PEF within one week. In general, APs based on SDs of symptom scores performed better than predefined absolute levels of symptoms. This judgment was based on lower NNTs for the former approach. For PEF using % pb resulted in considerably lower NNTs than using SDs.

The optimal symptom AP was a score that increased by more than two SDs more than the run-in mean, and this detected exacerbations 2.9 days before occurrence with 88.5% sensitivity, 86.3% specificity and a NNT of 24. For PEF, the optimally performing AP was a PEF <60% pb, which is also currently proposed by the British Thoracic Society as the threshold for commencing oral prednisone treatment (Table 13 in reference [5]). It had a sensitivity of 78.2%, specificity of 98.7% and a NNT of 3. However, it detected exacerbations only 1 day before their occurrence. The optimal combination (symptoms and PEF) comprised a symptom score increase of >2SDs plus PEF decrease to <70% pb. This combination detected exacerbations 1.4 days before their occurrence with 80.5% sensitivity, 98.3% specificity and a NNT of 4. Within a one week window, this symptom-PEF combination detected exacerbations 4.1 days (mean) before their occurrence with a sensitivity of 85.1%, specificity of 97.2% and a NNT of 6 (Table 2).
The performance characteristics of optimal APs in the validation dataset are presented in Table 3. In general, the sensitivities for each of the optimal APs differed somewhat from those obtained using the developmental dataset, whereas specificities remained similar. For each optimal AP, the number of days before the onset of an exacerbation at which the AP predicted future exacerbations was better in the validation dataset, i.e. between 0.4 - 1.0 day earlier.

For both versions of the AP recommended by the NHLBI, the combination of “appearance of any symptoms” *plus* PEF <80% pb performed best (see Table 3). It detected exacerbations 4.9 days before onset, with a sensitivity of 100.0% and specificity of 86.8%. However, the NNT is 43, whereas it is 12 for the optimal AP from the development dataset (see Figure 2).

The comparable data using the alternative definition of “use of oral prednisone” are also reported in Tables 2, 3 and 4 a-d. In general, sensitivities were considerably lower, overall accuracies were similar, early diagnosis was slightly later, but the NNTs were better.
DISCUSSION

The present study provides the most comprehensive data to date of the performance characteristics of a range of symptom and/or PEF thresholds at which patients might intervene to abort an asthma exacerbation or reduce its severity. For symptoms, a change of >2 SDs in a composite symptom score provided optimum outcomes. For PEFs, a decrease to <60% pb was optimal. However, an AP based on a combination of changes in symptom score (>2 SDs) and PEF(<70% pb) occurring during a one week period performed even better. This combination predicted exacerbations five days before their occurrence, thus allowing sufficient time to intervene, whilst the NNT remained low.

Previously, in a Cochrane review, Powell et al. compared the use of Written Asthma Action Plans (WAAPs) based on symptoms with those based on PEF [12]. Results showed these were equivalent with regard to outcomes i.e. hospitalizations or unscheduled doctor visits. Our data indicate that combining symptoms and PEFs provide added value. Clearly, it is not practical for patients to do the necessary calculations, and therefore in practice, an AP based solely on PEF <60% pb might be optimal. Nevertheless, with the advent of internet-based applications (“Apps”), the use of seemingly complex APs is now feasible [13]. Although compliance with paper diary recordings is generally poor [14], such an approach is feasible with electronic recordings [15] and of particular relevance in patients with difficult or brittle asthma.

The fact that a “both/and” combination of symptoms and PEF performed better than single APs is not surprising. Even with good asthma control, symptoms and PEFs may vary discordantly, and one of these parameters may change in isolation, especially in “poor perceivers”. Action points with threshold levels based solely on symptoms or PEF, are susceptible to these variations. Using a more stringent threshold, such as ‘PEF <60% pb’ can solve this issue, but has the disadvantage of late detection of an imminent exacerbation.
Therefore using a one week window for the symptoms plus PEF provided the best AP since it detected exacerbations 5.1 days before occurrence, at only a slight cost in specificity and NNT. To assess whether symptoms or PEF drive earlier detection using the AP with a one week time window, we performed a subgroup analysis of the 74 predicted exacerbations. There was no consistent pattern as to whether changes in symptoms preceded PEFs, or vice versa. Symptoms occurred earlier in 25, the threshold for PEF changes was reached earlier in 23, and in 26 there was no discordance.

Previously, Gibson analysed nine different APs and showed that QCA of daily PEFs performs better than percentages of personal best PEF (in contrast to the present data) or percentage predicted of PEF [7]. In Gibson’s report the optimal QCA action point detected 91% of exacerbations and falsely predicted an exacerbation in 23% of periods of normal control. Tattersfield analysed the false positive rate of action points based on the median values of PEF and symptoms at 2 days before the start of an exacerbation. They found a false positive rate of 6.4% using the advent of nighttime symptoms, 26% for morning PEF and 30% for daytime symptoms [16]. Thamrin analysed daily fluctuations in PEF, and by calculating conditional probabilities of future decreases in lung function, predicted the risk of exacerbations with a sensitivity of 68.8% and specificity of 67.4%. The AUC was 0.85, which is only slightly lower than AUCs of most optimal APs in this study [17].

The time course of changes in symptoms and PEF that constitute an asthma exacerbation is important in determining the optimum time for intervention. If changes can only be identified after the time at which intervention is likely to be effective, then the rationale for using WAAPs would be weak. Previous data suggest that symptoms and PEF start declining 5-10 days before exacerbations [16, 18]. The changes in PEFs and symptom scores associated with exacerbations in our patients are illustrated in Figures 3a and b. Based on these findings, we systematically analysed the 7-day period preceding exacerbations. We
found that changes in the optimal APs occurred between 1.7 and 5.1 days before the defined onset of an exacerbation (see Table 4, online supplement). The onset of action of systemic corticosteroid is within 12-24 hours, and so the APs would be reached in sufficient time to allow for steroids to have a modifying effect. The effectiveness of quadrupling the dose of inhaled corticosteroids was recently investigated by Oborne et al [19], and might have resulted in greater clinical benefits if commenced at the times which were calculated to be optimal in our study.

Our study has several possible limitations. Firstly, we selected criteria for acceptable sensitivity and specificity (see Methods: statistical analysis), since we aimed to balance early detection of exacerbations against potential over-diagnosis. Secondly, the composite symptom score(s) used in the two studies were not externally validated. It is not certain whether applying QCA to alternative scoring systems such as the Asthma Control Questionnaire or the Asthma Control Test would give similar results [22, 23]. However, given the overall similarity between results using both of our datasets, there is reason to believe that QCA is a valid approach to optimizing APs, independently of the exact scoring system used. Thirdly, APs were based on parameters that were incorporated in the definition of an exacerbation. Our study was not designed to be explanatory but rather to model predictive performance, and as such is methodologically sound. Our definition of major exacerbations, i.e. either ER-visits or changes in PEF plus symptoms for ≥2 days, is in accordance with recent criteria for severe exacerbations [4]. Furthermore, in modified forms, our definition has been used in several previous studies [10, 11, 20, 21]. However, accepting that the definition of an exacerbation is important in the interpretation of our data, we performed additional analyses using “use of oral prednisone” as the definition of an exacerbation (see Tables 2-4). The order of optimal APs was similar with regard to early detection and NNT (see also Figure 2b). Using this definition, the sensitivity to detect
exacerbations was considerably lower when using PEF either solely or in combination with symptoms, whereas it was only slightly lower using symptoms alone (see Table 4, online supplement). This implies that the decision to administer prednisone depended more on symptoms than on PEF. Given that the sensitivity was <75%, and the NNT was high, we concluded that the analyzed APs did not perform well enough to predict exacerbations defined as “use of oral prednisone. Such events were generally less severe than the exacerbations defined a priori using composite symptom scores and PEFs. It is therefore arguable that our APs performed well in predicting events of higher severity and in which earlier intervention is clinically desirable.

In conclusion, the optimal action point for the early detection of asthma exacerbations consists of a >2SDs increase in a composite symptom score and a fall in PEF to <70% pb, occurring within a one week window. With the advent of handheld computer technology, there is potential to use these criteria more readily in day to day practice, and thus reduce the impact of exacerbations, particularly in patients with a history of frequent exacerbations. Prospective studies or further analyses using other published datasets should be carried out to confirm the present findings, and together, they should be used to revise and improve the empirical recommendations offered in current guidelines.
ACKNOWLEDGMENTS

The developmental and validation datasets were provided to the principal authors (PJH and JKS) with full permission to undertake additional analyses by DRT. There are no competing interests for any of the authors relating this article. The study was partly funded by a Short Term Research Fellowship awarded by the Netherlands Asthma Foundation.
REFERENCES

(1) O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. Lancet 2006;368:794-803.


(3) Global strategy for asthma management and prevention. Global initiative for asthma. 2006.


**Table 1.** Baseline characteristics of patients in the two studies.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>164</td>
<td>94</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>38 (range 18-64)</td>
<td>44 (range 12-73)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male = 73 (45%) Female = 91 (55%)</td>
<td>Male = 35 (37%) Female = 59 (63%)</td>
</tr>
<tr>
<td>Taking regular inhaled corticosteroids (%)*</td>
<td>None 8% 34% 36% 22%</td>
<td>0% 53% 45% 2%</td>
</tr>
<tr>
<td>Mean symptom score during run-in period (maximum score = 6.0)</td>
<td>0.55 (range 0-2.06)</td>
<td>0.56 (range 0-2.65)</td>
</tr>
<tr>
<td>Mean personal best PEF during run-in (l/min)</td>
<td>508 (range 305-755)</td>
<td>448 (range 230-705)</td>
</tr>
</tbody>
</table>

* Beclomethasone equivalent.
Abbreviations

AUC  = Area under the receiver operating characteristic curve
AP   = Action Point
NNT  = Number Needed to Treat
pb   = personal best
PEF  = Peak Expiratory Flow
QCA  = Quality Control Analysis
SD   = Standard Deviation of mean score
Tables 2 and 3.

*Early Detection* is a description of how many days before the onset of an exacerbation this action point will predict the future occurrence of the event. It was assessed by calculating the mean number of days that this action point’s thresholds were reached for the first time in the week preceding the exacerbation, from all predicted exacerbations.

*Sensitivity, specificity and accuracy* refer to this action point’s ability to correctly predict an exacerbation and how often exacerbations are missed or falsely predicted.

*AUC* is a measure of the overall accuracy of a prediction, with 1.0 representing a perfect prediction with 100% sensitivity and 100% specificity, and 0.5 representing a random guess and therefore the model has no predictive properties. In general, AUC values of less than 0.7 do not have clinical significance.

*NNT* is the number of times this action point is positive per predicted exacerbation. It is a measure of how often an intervention is applied unnecessarily to prevent one exacerbation.
Table 2
Performance characteristics in the development dataset of the optimal action points per category.

<table>
<thead>
<tr>
<th>Action point category and optimal criteria</th>
<th>Definition of exacerbation</th>
<th>Early Detection (days)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>AUC</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (&gt;2SD)</td>
<td>Symptoms PEFs</td>
<td>2.9</td>
<td>88.5</td>
<td>86.3</td>
<td>86.3</td>
<td>0.87</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>2.7</td>
<td>76.9</td>
<td>86.6</td>
<td>86.5</td>
<td>0.82</td>
<td>17</td>
</tr>
<tr>
<td>PEF (&lt;70% pb)</td>
<td>Symptoms PEFs</td>
<td>2.9</td>
<td>90.8</td>
<td>93.9</td>
<td>93.9</td>
<td>0.92</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>2.6</td>
<td>61.2</td>
<td>93.9</td>
<td>93.5</td>
<td>0.78</td>
<td>10</td>
</tr>
<tr>
<td>PEF (&lt;60% pb)*</td>
<td>Symptoms PEFs</td>
<td>1.0</td>
<td>78.2</td>
<td>98.7</td>
<td>98.6</td>
<td>0.88</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>1.2</td>
<td>38.1</td>
<td>98.7</td>
<td>98.0</td>
<td>0.68</td>
<td>4</td>
</tr>
<tr>
<td>Symptoms + PEF: same day†</td>
<td>Symptoms PEFs</td>
<td>1.4</td>
<td>80.5</td>
<td>98.3</td>
<td>98.2</td>
<td>0.89</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>1.4</td>
<td>47.6</td>
<td>98.3</td>
<td>97.7</td>
<td>0.72</td>
<td>4</td>
</tr>
<tr>
<td>Symptoms + PEF: within 1 week†</td>
<td>Symptoms PEFs</td>
<td>4.1</td>
<td>85.1</td>
<td>97.2</td>
<td>97.1</td>
<td>0.91</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>3.5</td>
<td>54.4</td>
<td>97.2</td>
<td>96.7</td>
<td>0.76</td>
<td>5</td>
</tr>
</tbody>
</table>

† For Symptoms and PEF on the same day the optimal combination consisted of a composite symptom score >2SDs of the mean plus PEF <70% of personal best

‡ For Symptoms and PEF within one week the optimal combination consisted of a composite symptom score >2SDs of the run-in mean plus PEF <70% of personal best, with a seven day time window being allowed for either threshold to become positive.

* Action Point advised by the British Thoracic Society [5]
Table 3  Performance characteristics in the validation dataset of optimal action points derived from the development dataset and of the NHLBI action point [2].

<table>
<thead>
<tr>
<th>Action point category and optimal criteria</th>
<th>Definition of exacerbation</th>
<th>Early Detection (days)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>AUC</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (&gt;2SD)</td>
<td>Symptoms PEFs</td>
<td>3.3</td>
<td>75.0</td>
<td>86.2</td>
<td>86.2</td>
<td>0.81</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>4.1</td>
<td>60.0</td>
<td>86.9</td>
<td>86.6</td>
<td>0.73</td>
<td>19</td>
</tr>
<tr>
<td>PEF (&lt;70%pb)</td>
<td>Symptoms PEFs</td>
<td>4.2</td>
<td>100</td>
<td>92.5</td>
<td>92.6</td>
<td>0.96</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>3.6</td>
<td>53.3</td>
<td>93.0</td>
<td>92.5</td>
<td>0.73</td>
<td>12</td>
</tr>
<tr>
<td>PEF (&lt;60% pb) *</td>
<td>Symptoms PEFs</td>
<td>1.8</td>
<td>100</td>
<td>97.6</td>
<td>97.6</td>
<td>0.99</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>2.3</td>
<td>18.7</td>
<td>97.5</td>
<td>96.6</td>
<td>0.55</td>
<td>12</td>
</tr>
<tr>
<td>Symptoms + PEF: same day</td>
<td>Symptoms PEFs</td>
<td>1.7</td>
<td>75.0</td>
<td>98.3</td>
<td>98.2</td>
<td>0.87</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>2.1</td>
<td>29.3</td>
<td>98.5</td>
<td>97.6</td>
<td>0.64</td>
<td>5</td>
</tr>
<tr>
<td>Symptoms + PEF: within 1 week</td>
<td>Symptoms PEFs</td>
<td>5.1</td>
<td>75.0</td>
<td>97.4</td>
<td>97.3</td>
<td>0.86</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>4.8</td>
<td>33.3</td>
<td>97.6</td>
<td>96.8</td>
<td>0.65</td>
<td>7</td>
</tr>
<tr>
<td>NHLBI criteria changes in Symptoms AND in PEF</td>
<td>Symptoms PEFs</td>
<td>4.9</td>
<td>100</td>
<td>86.8</td>
<td>86.9</td>
<td>0.93</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>4.0</td>
<td>70.7</td>
<td>87.5</td>
<td>87.3</td>
<td>0.79</td>
<td>16</td>
</tr>
<tr>
<td>NHLBI criteria changes in symptoms OR in PEF†</td>
<td>Symptoms PEFs</td>
<td>6.5</td>
<td>100</td>
<td>47.5</td>
<td>47.6</td>
<td>0.74</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>Use of prednisone</td>
<td>6.1</td>
<td>100</td>
<td>48.2</td>
<td>48.8</td>
<td>0.74</td>
<td>46</td>
</tr>
</tbody>
</table>

* Action point advised by the British Thoracic Society [5]

Since the NHLBI action point can be interpreted in two ways, we provided both: ∫ appearance of any symptoms plus PEF <80% pb; † appearance of any symptoms or a PEF<80%.
Figure 1. This figure illustrates the use of action points in an 8 week peak flow chart with an exacerbation half-way. The dotted lines indicate the thresholds of potential action points, on the left based on % of personal best PEF, and on the right based on individual standard deviations for PEF. The observation period is divided in weeks before and during the exacerbation, and weeks of normal control, respectively coded as pre-exacerbation weeks and stable weeks. In this example, we have highlighted the Action Points PEF <70% pb and PEF <-3 SD. The Action Point PEF <70% pb is reached twice, once as a false positive in a stable week and once accurately two days before the exacerbation in the pre-exacerbation week. The Action Point PEF < -3 SD is never reached in this example, representing a false negative prediction for the pre-exacerbation week (marked X).
Figure 2 a, b.

*Above figure*

The number of days the exacerbation is predicted before its occurrence is plotted against the (potential) number needed to treat (NNT) in order to prevent one exacerbation, for a series of different action points. The lower left corner represents the optimal action point, i.e. early prediction and low NNT. In Figure 2a exacerbations are defined using the definition described in the Methods section, in Figure 2b exacerbations are defined as a “use of oral prednisone”.
Below figure

1. Symptoms >2SD
2. PEF <70% pb
3. PEF <60% pb
4. Symptoms >2SD + PEF <70% pb
5. Symptoms >2SD + PEF <70% pb within one week
6. NHLBI

Figure 2a and 2b show similar results, although the differences are larger in Figure 2a. Action points 3, 4 and 5 perform similarly, with a slight increase in NNT for each day the exacerbation is diagnosed earlier. “Optimal” depends on the trade-off between NNT and early detection. To allow sufficient time to successfully intervene, we opt for number 5. Action point 1, 2 and 6 perform considerably worse, due to the high NNTs.
Figures 3a and 3b. Changes in PEF (a) and symptom scores (b) from day -14 to day +10 before and after an exacerbation, using the mean PEF and symptom score data from each exacerbation in the development dataset.