

REVIEW

Monitoring response to treatment in asthma management: food for thought

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Summary

Asthma is a chronic inflammatory disorder of the airways that is characterized by episodic symptoms. In this regard, asthma management has classically involved periodic re-assessment by the health-care provider, during which therapy is altered mainly based on clinical and physiological parameters, such as assessment of symptoms, spirometry and peak expiratory flow monitoring. In this context, various markers of airway inflammation (e.g. eosinophils in the induced sputum, nitric oxide in the exhaled air) have been proposed to assess the severity of asthma and to adjust the therapy accordingly. The evaluation of airway hyper-responsiveness with different stimuli has also been suggested as a new tool to monitor asthma. However, the lack of definite relationships between airway inflammation and asthmatic symptoms strongly limit the use of markers of asthma severity in the clinical setting. Therefore, the need of new tools to assess the severity of asthma is raised. The ideal measurement employed to establish the proper asthmatic therapy should be safe, non-invasive, easy to perform, reproducible and accurate, and have the capability to monitor the changes induced by the therapeutic interventions. A careful review of the available techniques, and the evaluation of their sensitivity and specificity in the clinical setting is warranted.

Introduction

Asthma is prevalent in developed countries [1] and causes an economic burden to patients, their families and society [2]. Current international guidelines for asthma management outline similar goals of treatment [3–7], and emphasize maintenance control as identified by: (1) minimal or no day and night-time symptoms, (2) best possible lung function, (3) minimum or no asthma exacerbations, (4) minimum or no need for relieving bronchodilator, and (5) minimum or no limitation of activities. This level of control should be maintained with the least possible medication. Finally, these guidelines also focus on the reduction of airway inflammation as a central component of asthma control.

From these recommendations, therefore, one could assume that little or no inflammation is present in the airways of an individual whose asthma is controlled. This is in part supported by evidence that measurements of airway inflammation can correlate with symptoms [8–11], airflow limitation [12–14] and airway hyper-responsiveness (AHR) [15–19], although the overall relationships are poor [20]. However, the results of a recent study are suggestive of persistent airway inflammation during clinical remission of atopic asthma [21]. In addition, although it is clearly emphasized that monitoring airway inflammation is critical to achieve effective control,

the current guidelines fail to indicate what type of monitoring is truly useful.

In this article, we will review the use of spirometry and of peak expiratory flow (PEF) monitoring according to current asthma management guidelines. The use of new measurements of bronchial responsiveness and inflammatory markers in induced sputum or levels of nitric oxide (NO) and breath condensate in exhaled air as indicators of airway inflammation will also be discussed in detail. In addition, we will critically address the question whether these new measurements to monitor asthma should be integrated into asthma guidelines and/or clinical practice. Some of these techniques have become accepted in clinical practice without rigorous and careful evaluation. If a new measurement is to be used to improve asthma management, it should be non-invasive or relatively non-invasive, easy to perform and safe, reproducible, accurate, able to reliably discriminate different airway diseases and their severity, and be able to monitor changes after interventions. Finally, we will address the use of questionnaires and diary cards assessing asthmatic symptoms and quality of life in optimizing asthma control.

Monitoring response to treatment in asthma management: what is the role for spirometry?

Although the diagnostic approach and the characterization of the asthmatic condition are based on the evaluation of symptoms, the objective assessment of lung function represents an important cornerstone in asthma management. In this context, spirometry is the most widely accepted measurement of lung function, and its use is extensively

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recommended by international guidelines [3–6]. The outcome of the spirometric manoeuvre provides a direct assessment of airflow limitation, thus offering useful indications for the physician's clinical choice on the individual patient. The strength of this method is based on its simplicity and high reproducibility. This is of great importance when therapeutic interventions are to be properly assessed. However, it should be considered that, in asthma, the magnitude of airway obstruction may vary considerably from time to time, and that single measurements of lung function may not reflect the overall severity of the condition [22]. Spirometry reflects specific mechanical features of the respiratory system: forced expiratory flow is determined by the elastic recoil of the lung, as well as by the resistance of the airways and the degree of airway compression during the forced manoeuvre. The spirometric manoeuvre is not able to distinguish between a small vs. a large airway involvement. The issue is whether, and to what extent, inflammation of the small airways alters airway physiology and causes asthmatic symptoms. If, on the one hand, asthma is considered mainly a disease of large airways, on the other hand, increasing histopathologic evidence of inflammation within the small airways is available [23–25]. Structural changes occur in both large and small airways in fatal asthma, but predominantly in small airways in non-fatal asthma [26]. Excessive narrowing of small airways could lead to air trapping [27], which represents one of the most serious abnormalities in asthma. There is, therefore, a pressing need for measures of small airway function. A functional parameter characterized by a decreased vital capacity and forced expiratory volume in 1 s (FEV₁) and increased residual volume, with normal total lung capacity has been proposed as a spirometric index of small airway impairment [28]. Moreover, since the interdependence between airways and parenchyma allows for airway diameter to increase with increasing lung volumes, inflammation and oedema would blunt this mechanism by unlinking the parenchyma from the airways. In this regard, the role of lung inflation on airway caliber has been widely established [29–33]. In healthy subjects, lung inflation has been demonstrated to exert a bronchodilatory function, which tends to decrease with increasing asthma severity, as assessed by salbutamol usage and symptom score [34]. In this study, we also demonstrated the lack of an association with FEV₁ and FEV₁/FVC, suggesting that the bronchodilatory effect of deep inspiration might be a better descriptor of asthma severity. This is further confirmed by the observation that the bronchodilatory ability of lung inflation significantly correlated with the rate of exacerbations over a 6-month follow-up. On this basis, the role of spirometry should be restricted to the diagnostic evaluation of the asthmatic subject, or in the context of epidemiological studies.

Monitoring of peak expiratory flow in asthma management: is it really useful?

Based on the variability of airflow obstruction in asthma, strong emphasis has been given to the use of portable PEF meters. PEF measurements have been proposed as a practical alternative tool to more complex and time-consuming measurements to assess diurnal variation of lung function in asthmatics. The rationale of this test is that the more often the

lung function is measured, the greater the probability that it will reflect the true pattern of asthma in a given patient. The advantage of PEF measurements is that this simple manoeuvre can be performed in the home setting at a low cost.

The clinical importance of PEF measurements lies in the fact that PEF recording is thought to mainly reflect lung function variability. Indeed, asthmatics show greater diurnal variation in PEF than normal subjects [35–38]. Most importantly, PEF variability relates to AHR [39, 40] and, for such reason, it has been proposed as one of the most important tool to monitor asthma [3]. Thus, reducing PEF variability with treatment is to be considered a major accomplishment in asthma management. However, there are a number of well-conducted studies showing that a wide range of diurnal variation of PEF occurs among asthmatics with disease of similar severity, and there is considerable overlap in diurnal variation between patients with asthma of different severity [41, 42]. This poor ability to discriminate may result from the fact that PEF primarily reflects the calibre of larger airways, and the correlation with other indices of lung function (especially those reflecting the medium and smaller airways) is generally poor, except in subjects with severe asthma [43, 44]. In addition, it must be considered that measurements of PEF at home, although convenient for the patient, are extremely vulnerable to deliberate or accidental manipulation of the results [45]. Finally, as it has recently been pointed out [46], commercially available peak flow meters may not be accurate enough to monitor asthma variability: thus, improving the accuracy of PEF meters is mandatory.

An important question is whether the use of home monitoring of PEF adds further information to what may be learned from a diary or from clinical observation. A large Dutch step-up study, in which inhaled corticosteroids were added to treatment according to changes in PEF measurements, showed poor concordance with other parameters of asthma severity, and the authors concluded that home recording of PEF alone may not be sufficient to monitor asthma reliably [47]. In the study by Uwyty et al. [48], PEF measurement was shown to add little to the daily recording of asthma symptoms in children and young people with moderately severe asthma and was too insensitive in those with milder asthma. This finding has been confirmed in adult patients with moderate-to-severe asthma [49]. In a year-long study of asthma self-management plans in general practice, Charlton et al. [50] concluded that with an appropriate treatment plan and advice from the clinic there is no need for PEF meters. Moreover, a recent randomized single-blind study involving six European centres has shown that the use of PEF as a guide to titrate the dose of glucocorticosteroids in adult asthmatics with moderate-to-severe disease led to a substantial increase in the use of inhaled glucocorticosteroids without improvement in symptoms and/or lung function [51]. That PEF variability alone is not satisfactory in guiding the therapeutic need in asthma is also clearly suggested by the work of Goldstein et al. [52]. The investigators compared PEF variation with post-bronchodilator FEV₁ and responses to methacholine bronchoprovocation challenges, and concluded that relying on PEF variability alone could lead to underdiagnosis and undertreatment in patients with asthma. Taken together, these studies indicate that there is little

evidence to support a central place for PEF measurements in the guidelines for asthma management.

Measurement of bronchial hyper-responsiveness: can be exploited to guide asthma management?

Bronchial hyper-responsiveness (BHR) is a central physiological characteristic of asthma and can explain many of its clinical features [53]. Although the pathogenesis of BHR appears a complex phenomenon, a body of evidence has demonstrated the central role of airway inflammation in increasing airway responses to bronchoconstrictor agents [13]. In this context, individual adjustment of anti-asthma medications, which is mainly based on measurements of symptoms and airflow limitation, could benefit from the use of bronchoprovocation challenge test.

Bronchoprovocation challenges are performed by employing direct stimuli, such as methacholine or histamine, which cause airway obstruction by acting on the smooth muscle, and indirect stimuli, such as adenosine, bradykinin or exercise, which induce airway obstruction by activating cells other than the effector cells [54]. Although the overall impression is that the worse the hyper-responsiveness, the worse the asthma [53, 55, 56], there is considerable overlap among asthmatics with disease of different severity [57, 58]. Indeed, a number of studies have failed to show any relationship between asthma severity and bronchial responsiveness; in studies on paediatric population, as many as one-third of children with marked hyper-responsiveness required no medication [59, 60]. These conflicting data imply that BHR alone is reflective of some, but not all, features of the asthmatic phenotype. Alternatively, asthma could be depicted as a syndrome with a heterogeneous presentation, in which BHR is the underlying abnormality. Another factor must be taken into account, that is, the use of arbitrary criteria to define an abnormal response, which might easily lead to confusion. The interpretation of bronchoprovocation results should include the level of lung function and the probability of asthma before the test is performed, and the sensitivity and specificity of the bronchoprovocation test should be always considered [61].

With respect to monitoring asthma, there is some evidence to suggest that repeated measurements of bronchial responsiveness over a realistic time frame reflect changes in asthma severity occurring spontaneously or in response to treatment. Woolcock et al. [62] performed repeated measurements of bronchial responsiveness in adult asthmatics over a 1–2-year period of carefully monitored treatment and showed a marked reduction in bronchial responsiveness, although only three of the 13 patients achieved near-normal levels of reactivity. Josephs et al. [63] followed eight children and 12 adults with asthma for a period of 12–18 months and performed bronchial challenges with methacholine every 2–3 weeks. In 14 out of the 20 patients, no clear relationship was seen between exacerbation of asthma and the severity of BHR. Likewise, another long-term study showed that the individual correlation coefficients between bronchial responsiveness to methacholine and the percent of symptom-free days was very poor in asthmatic children ($R = 0.27$) [47]. Conversely, a large cross-sectional study in paediatric asthma demonstrated that BHR to methacholine may serve as a valuable tool for discriminating disease severity [64]. A recent

retrospective analysis of 487 adult asthmatic patients came to similar conclusions, namely that methacholine is a sensitive index of BHR and is closely related to asthma severity [65]. Given that the available evidence appears rather conflicting, the hypothesis that BHR could be useful as an indicator of disease severity requires further research.

The effect of treatment on bronchial responsiveness to histamine or methacholine has mainly been studied in relation to the short-term effect of inhaled glucocorticosteroids. The results have been quite consistent and, of the published studies with adequate data, the mean decrease in bronchial responsiveness to histamine or methacholine is estimated as approximately 1–2 doubling doses. The implication of such a change is not necessarily very impressive, since a decrease in responsiveness of 2–3 doubling doses still leaves all but the patients with the mildest asthma in the very hyper-reactive range. Sont et al. [66] examined the capability of BHR to guide therapy. The authors compared a 2-year treatment based on current recommendations (symptoms, PEF variability and clinic FEV₁) with asthma management in which the severity of BHR was also taken into consideration. The results of this study showed that integration of a standard asthma management plan with regular assessment of bronchial responsiveness led to a significant reduction in the overall mild exacerbation incidence throughout the study. However, this was obtained at the price of more than twice the daily intake of inhaled glucocorticosteroids (800 vs. 300 µg/day) and unfortunately the therapeutic need of the mild asthmatics in the reference strategy group was guided by PEF variability and symptom scores which, as we discussed above, are poorly satisfactory in asthma management. From the same study, the finding of a reduction, even if modest, in thickness of the subepithelial collagen layer of asthmatic airways obtained only with the bronchial responsiveness-based management, poses the important question of whether the optimal therapy should aim at reversing remodelling changes of airway walls, in order to prevent irreversible airflow obstruction and the accelerated decline of lung function. It is important that future work concerning optimal glucocorticosteroid dosing in asthma management should also take into account long-term studies, which reflect changes in remodelling.

In this context, it is likely that bronchoprovocation challenges that use indirect stimuli better reflect the complex heterogeneity of asthma pathogenesis [67]. For example, bronchoprovocation with adenosine 5'-monophosphate (AMP) appears to offer substantial advantages over other non-invasive surrogate markers of airway inflammation [68]. Compared with other non-invasive surrogate markers of airway inflammation (including methacholine), monitoring of BHR with inhaled AMP appears to have the selective ability to probe changes in airway inflammation and it has been shown to be very useful when evaluating the effectiveness of different treatment regimens with inhaled glucocorticosteroids (type, dose, inhalation device, particle size, etc.) [68] or when assessing the effect of immunotherapy on non-specific BHR [69]. Moreover, we have recently demonstrated that, compared with PC₂₀ methacholine and sputum eosinophilia, BHR to inhaled AMP is an early and sensitive indicator of the beneficial anti-inflammatory effects of topical glucocorticosteroid GCS [70] (Fig. 1). In relation to this, the recent article by Prieto et al. [71] assessing the utility of the

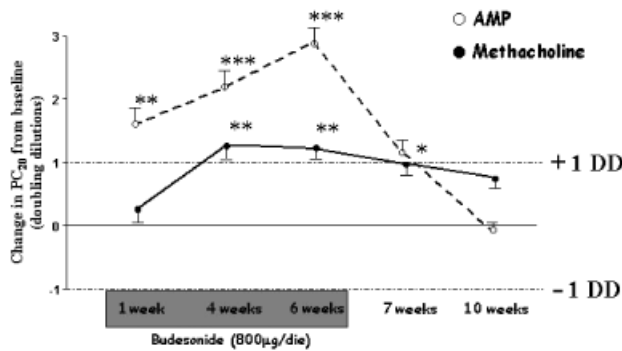


Fig. 1. Comparative changes in PC₂₀ methacholine (closed circles) and PC₂₀ AMP (open circles) expressed as mean ($\pm$ SEM) doubling dilutions (DD) before, during and after discontinuation of budesonide treatment. For PC₂₀ AMP, a significant difference from baseline was already observed at one post-budesonide, whereas no significant change was observed at any time-point after treatment discontinuation; for PC₂₀ methacholine a significant change was observed at 4 and 6 weeks post-budesonide and at week 7, 1 week after discontinuation of budesonide. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (post-treatment vs. baseline). Data adapted from reference [70] with permission.

determination of airway responsiveness to inhaled AMP as a predictor for safe dose reduction of inhaled GCS, in selected patients with asthma, is an important advance.

Taken together, these studies indicate that AMP may be one of the most accurate guide to monitor inhaled GCS requirements in asthma and to establish the appropriate dose needed to control airway inflammation. However, whether introducing this approach for disease monitoring would improve patient day-to-day asthma is far from certain and requires appropriate validation by evaluating prospectively a treatment algorithm that incorporates AMP responsiveness in a controlled clinical setting.

Measuring cells in induced sputum: are there evidences for its use in asthma management?

Recent research has optimized methods to process spontaneous and induced sputum for inflammatory cell counts to investigate airway inflammation. The results are valid, repeatable, and responsive to change [72–74]. Sputum induction, being relatively non-invasive can be applied at random and repeatedly to examine airway inflammation and to investigate anti-inflammatory properties of drugs in clinical trials [75]. Simple assessment with clinical and physiological parameters, in some situations, may not be enough to guarantee adequate asthma management. Indeed, results from some recent studies suggest that markers of airway inflammation measured in sputum might have a place in clinical practice of asthma and other airway diseases. Possible applications are severe uncontrolled asthma with recurrent exacerbations, mild asthma that might have persistent eosinophilic inflammation, asthma in association with chronic airflow limitation, moderate-to-severe acute asthma exacerbations and when an occupational cause is possible.

Although not based in sounded evidence, recent studies suggest that the presence of a sputum eosinophilia can predict response to inhaled steroids [76] and that a management strategy that is planned to control eosinophilic inflammation

as well as symptoms would result in fewer exacerbations than a traditional asthma management plan. At present, there is one study and two published abstracts that have investigated this hypothesis. Green et al. [77] compared the effect of a management strategy aimed to normalize sputum eosinophil counts as well as minimizing symptoms (sputum group) with a standard clinical approach based on the British Thoracic Society asthma guidelines (BTS group) in 74 subjects attending a specialist clinic for asthma management. Treatment decisions in the BTS group were based on traditional assessments of symptoms, PEF, and β_2 -agonist and in the sputum group were based on the principle of maintaining a normal sputum eosinophil count ($<3\%$) with a minimum dose of anti-inflammatory treatment. Clinical and functional outcomes were similar in both groups; however, subjects randomized in the sputum group experienced significantly fewer cumulative number of asthma exacerbations than patients in the control group (35 vs. 109, $P = 0.01$) and significantly fewer patients were admitted to hospital with asthma (1 vs. 6, $P = 0.047$). Importantly, these results were obtained without any increase in the average daily dose of inhaled or oral corticosteroids in the sputum strategy compared with the standard strategy. The authors concluded that the use of induced sputum in targeting anti-inflammatory treatment appears to result in improved patient management. We also have finished a 2-year study designed to compare the effects of controlling airway inflammation on top of clinical guidelines with those of the standard practice based on the Canadian Guidelines. The results of the first year in the first 100 patients [78] have shown that a strategy aimed to control airway inflammation is able to reduce the exacerbation rate by 50%. Moreover, this benefit was also obtained without any additional increase in the mean dose of steroid needed to keep the patients controlled. One further study [79] has shown similar findings. Taken together, the results of these reported studies indicate that regular monitoring of airway inflammation by sputum induction may optimize treatment and reduce the occurrence of asthma exacerbations. However, extrapolation of these findings to patients with milder disease managed in primary care setting requires further study.

Another area where the examination of sputum can help is in patients with chronic airflow limitation either due to long-standing asthma or COPD. In this group of patients, the presence or absence of sputum eosinophilia relates closely to whether a short therapeutic benefit is or is not obtained with corticosteroid treatment. There are few controlled trials that have shown that when chronic airflow limitation is associated with eosinophilic inflammation, a significant improvement in FEV₁ and quality of life is achieved after a course of prednisone or inhaled steroid in comparison with the response in patients with non-eosinophilic inflammation [80–82].

Additionally, sputum examination also may help to sort out optimum treatment in patients with another aspect of acute asthma exacerbations. Treatment of moderate-to-severe asthma exacerbations usually requires prednisone treatment and represents an economic burden to the health system and for patients' quality of life [83]. There is compelling evidence to demonstrate that during exacerbations the inflammatory response is not homogeneous, with treatment failure up to 30% of the cases. However, there have been no published

studies evaluating the response to corticosteroid and the inflammatory response. We have evaluated this in 46 episodes of moderate-to-severe asthma exacerbations reported by the treating physician as requiring prednisone treatment [84]. Baseline measurements with sputum examination were performed before any treatment with oral steroids. Patients were followed for 1 week and tests were repeated at day 7. The main outcomes were symptoms recovery measured by the asthma control questionnaire (ACQ), post-bronchodilator FEV₁ and inflammatory cells in sputum. Seventy-four percent of exacerbations were eosinophilic, and after treatment with systemic steroids there was a significant reduction in sputum eosinophils and no effect in the proportion of sputum neutrophils. In the eosinophilic group, the decreasing in sputum eosinophils was accompanied by significant improvements in post-bronchodilator FEV₁ (43%, 0.6 L) and in the ACQ (1.5 U). In the non-eosinophilic group, the response was not clinically significant. The post-bronchodilator FEV₁ increased 8% (0.1 L) and the ACQ (0.48 U), a difference not clinically important.

Finally, in the diagnosis of occupational asthma that requires as much objective confirmation as possible, studies have shown that there is an increase in sputum eosinophils during periods at work, followed by a decrease during periods away from work and the addition of measurements of airway inflammation can increase the accuracy of establishing the final diagnosis [85].

These results clearly indicate a place for examining sputum inflammatory cells in asthma management. Although sputum measurements are reliable and valid, they require trained staff under ongoing quality control and this might not be easily available in primary or secondary care. This can be made possible by having the procedure carried out by a local reference centre where the expertise is available and, most likely, by future simplification of the processing with the potential for automated cell counts. With this in mind, there is a need for well-designed studies using induced sputum in clinical practice. These studies should increase the chances of a better understanding of asthma pathophysiology and management of not only asthma, but also other airway diseases where inflammation is involved.

Measuring exhaled nitric oxide: where do we stand?

Since the initial discovery that NO is detectable in the expirate of humans and the subsequent demonstration that individuals with asthma exhaled higher levels of NO as compared with healthy subjects [86–90], there has been intense investigation of exhaled breath components as potential markers of airway inflammation in asthma and other conditions. While this activity has predominantly focused on the role of exhaled markers as features of the pathobiology of asthma in the laboratory setting, emerging data suggest that measurement of exhaled NO and possibly exhaled breath condensate (EBC) may play a role in clinical asthma management. Specifically, exhaled markers may be useful for asthma diagnosis, have a role in identifying patients with unstable disease, and possibly predict future response and failure of asthma therapy.

In the light of the well-established observation that the fraction of expired nitric oxide (F_ENO) is elevated in asthma, and the more recent finding that F_ENO correlates with other

characteristic features of asthma including AHR and sputum eosinophils, F_ENO has been suggested to be a component of the asthmatic phenotype [87, 91–96]. In support of this concept is the finding that F_ENO is a robust discriminator between asthmatic and non-asthmatic individuals in well-characterized study populations. In this regard, elevations in NO have been reported to be 75–85% sensitive and 71–87% specific for a diagnosis of asthma depending on the study and cut-off value selected [97–99]. In one study, the discriminatory properties of F_ENO for a diagnosis of asthma were as robust as those historically reported for a single assay of CPK-MB for a diagnosis of myocardial infarction (Fig. 2) [98, 100].

Exhaled NO levels appear to indicate the level of disease stability. Sippel et al. [101] reported that F_ENO is higher in asthmatics with features of poor control including recent symptoms and daily rescue medication use as compared with asthmatics with more stable disease. Exhaled NO is also elevated in the context of asthma exacerbations requiring emergency treatment or hospitalization [89, 102, 103]. In this acute setting, administration of glucocorticoids reduces F_ENO and this reduction parallels improvements in symptoms and measures of airflow. In this regard, NO has been proposed to have a role in discriminating patients with asthma from those with other causes of acute dyspnoea, but this has not yet been formally studied [103].

Asthma therapies can also influence exhaled NO levels when administered on a longer-term basis. Consistent with the view that NO reflects ongoing airway inflammation, anti-inflammatory medications such as systemic or inhaled glucocorticoids and leukotrienes modifiers reduce exhaled NO, while bronchodilators have no such effect [89, 104–113]. When examined over several weeks, the effects of inhaled corticosteroids on exhaled NO parallel the effects of these

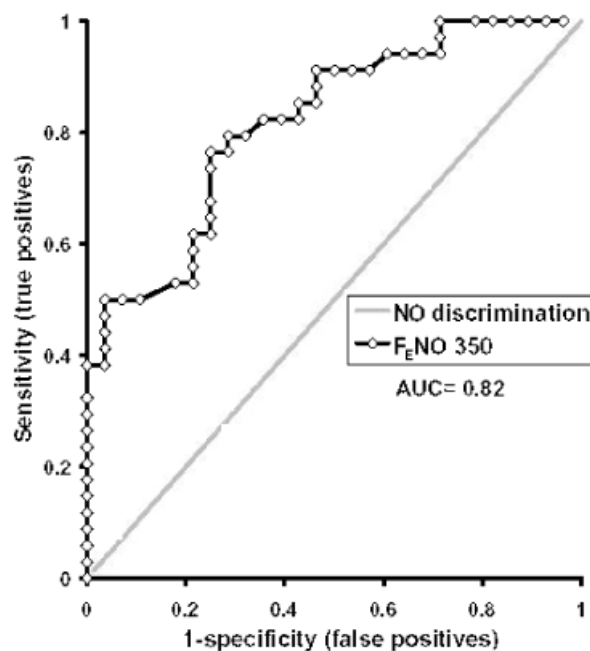


Fig. 2. The diagnostic properties of exhaled nitric oxide (NO) with respect to asthma are robust. The area under the receiver-operating characteristic curve for NO collected at 350 mL/s is 0.82. Data adapted from reference [98] with permission.

medications on other markers of airway activity including sputum eosinophil numbers and methacholine PC₂₀ [114, 115]. It is important to note, however, that the reduction of NO levels occurs very rapidly after the institution of anti-inflammatory therapy and thus may precede changes in other surrogate markers of airway inflammation [116].

In the light of its association with airway inflammation, NO has been investigated as a predictive marker of clinical outcome in asthma. Recent data suggest that elevations in F_ENO predict a greater likelihood of response to both inhaled and oral corticosteroids. Szeffler et al. [117] have reported that asthmatics experiencing a 15% improvement in FEV₁ following a course of inhaled corticosteroids had significantly higher F_ENO prior to treatment than similarly treated asthmatics whose FEV₁ subsequently improved by <5%. Notably, sputum eosinophilia was not predictive of the response. The superior predictive capacity of NO for an improvement in lung function as compared with sputum eosinophilia has also been shown in the setting of oral corticosteroids treatment [118].

Several authors have explored the ability of exhaled NO to predict asthma deterioration during tapering of inhaled corticosteroids. In the majority of studies, while exhaled NO rose as inhaled corticosteroids were reduced or stopped, these elevations were unable to specifically identify subjects who subsequently went on to develop an exacerbation [119, 120]. On the contrary, a recent study by Jones et al. [121] reported that F_ENO > 15 p.p.b. has a positive predictive value of 83% for predicting deterioration at the subsequent visit. Applying the poor sensitivity and specificity of NO for predicting exacerbations reported by Jones et al. (50% and 65%, respectively) to the more commonly demonstrated rate of deterioration with inhaled corticosteroid withdrawal of 35%, results in a positive predictive value of 44% [115, 122]. Thus, it appears that the currently available data do not clearly support a role for F_ENO in predicting exacerbations occurring during the tapering of inhaled corticosteroids. In contrast, preliminary data suggest that exhaled NO may be a robust predictor of asthma deterioration occurring during *continued* inhaled corticosteroid therapy (A. Deykin, personal observations). Whether elevated exhaled NO in this setting may be considered as a marker of steroid-resistant inflammation or non-compliance with prescribed medication is not clear.

Exhaled breath condensate: ready for clinical use?

When gas is exhaled into a cooling chamber, the condensate formed (containing water vapour and droplets of airway lining fluid) can be collected and analysed. Recent investigation of the composition of the EBC has demonstrated concentrations of several biological mediators that vary in health and disease states. For example, elevated levels of leukotrienes, 8-isoprostane (a marker of oxidative stress), and hydrogen ions have all been demonstrated in asthma [123–125]. As with exhaled NO, these elevated levels have been reported to decline with administration of inhaled corticosteroids. However, as presently available techniques for the collection of the expirate and the quantification of recovered substances have not been standardized, the utility of these

measurements outside of the research setting cannot yet be established.

Measuring asthma control: symptoms and quality of life

In clinical practice, the achievement of an acceptable clinical control of asthma is usually based on one or more functional outcomes, rather than on a comprehensive clinical assessment. This could represent a limitation of asthma monitoring. Recently, validated measurements such as the Asthma Control Questionnaire and Asthma Control Diary have been introduced in the clinical practice to optimize asthma treatment. The Juniper Asthma Quality-of-Life Questionnaire (AQLQ), the Medical Outcomes Survey Short Form 36 (SF-36), and the St George's Respiratory Questionnaire (SGRQ) have shown high reliability and validity in the asthmatic population and high level of responsiveness. Diary cards including global questions that assess asthma severity (e.g. 'How has your asthma been today?') and asthma impact (e.g. 'How much effect has your asthma had on your life today?') have also been used in asthmatics, and were demonstrated to correlate with AQLQ and SGRQ [126]. However, the responses to these questions were found to depend on their wording, which limits the usefulness of this tool as a reliable measure of treatment efficacy [126].

In addition to assessing the severity of asthma, the above-cited questionnaires describe aspects of quality of life in individuals with asthma. This is an important aspect of managing asthma, considering that quality-of-life information reflect the impact of the disease on the everyday life. Quality-of-life measurements can be more responsive to clinical changes than conventional clinical measures [127]. Therefore, adjusting the treatment on the basis of this integrated approach can be more accepted by the patient and may provide a better control of the disease [128, 129]. In conclusion, a composite measure of clinical control of asthma is advocated.

Which technique?

Unfortunately, the available evidence discussed above does not clearly justify asthma monitoring by any one of the techniques reviewed. Advantages and limitations for each method are summarized in Table 1. Neither symptoms, diurnal PEF measurements, bronchoprovocation challenges, nor inflammatory markers meet the criteria that are needed for a new tool to be added to the management of asthma. What patients and physicians treating asthma need is an objective measure of the severity of the disease in order to decide (1) what type of treatment to apply and (2) how the patient is responding to treatment. There is no doubt that, from a clinical standpoint, the optimal assessment method does not exist. In this respect, there are no conclusive studies at present on which to base a definitive answer as to the best methods of monitoring asthma. Despite the emerging view that surrogate markers of airway inflammation may have useful clinical applications, specific recommendations for these will require further work. It is important that well-planned and well-conducted large clinical trials must be performed to demonstrate that information gained from this test will lead to improved patient management. Overall, a

Table 1. Advantages and limitations for each procedure are described

Procedure	Advantages	Limitations
Spirometry	Simplicity, high reproducibility	Poor correlation to severity
PEF	Simplicity, low cost	Poor correlation to severity, risk of accidental/deliberate manipulation
Mch bronchoprovocation	High reproducibility, high sensitivity for diagnosis	Poor correlation to severity, time consuming
AMP bronchoprovocation	Higher sensitivity for inflammation	Lack of validation
Sputum induction	High reproducibility	Time consuming
	High sensitivity for inflammation	Need for trained staff
NO and EBC measurements	High sensitivity for inflammation	Lack of validation
Asthma questionnaires, diary cards	High reliability	Dependent on the responder
	Simplicity	

PEF, peak expiratory flow; AMP, adenosine 5'-monophosphate; EBC, exhaled breath condensate.

composite measure of clinical control that includes a comprehensive assessment of asthma is warranted.

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