

# Monitoring asthma status

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## Purpose

Asthma is a chronic disorder of the airways involving inflammation and airway hyper-reactivity. Clinical diagnosis and monitoring of asthma must incorporate the immunological, biochemical, and histological changes of a chronic disorder, while recognizing acute phenotypic changes in order to optimally tailor therapeutics to each individual.

## Recent findings

Articles published within the previous 18 months are summarized in this article in order to present an up to date review of the latest findings regarding the monitoring of asthma. The articles encompass a wide array of specialties from basic research and histology to clinical medicine as well as community medicine and nursing.

## Summary

Exciting new advancements in the monitoring of asthma continue to unfold. Potentially new diagnostic and monitoring tools are highlighted in this study. Continued investigations may enable a select few methodologies to reach clinical utility in the ongoing monitoring and treatment of patients with asthma.

## Keywords

asthma, exhaled nitric oxide, monitoring

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## Introduction

Asthma is a chronic inflammatory disorder characterized by airway hypersensitivity and airflow obstruction. Patients with poor asthma control experience episodes of exacerbation and develop worsening breathlessness, dyspnea, wheeze, chest tightness, and cough. The impact of these symptoms can range from limitations on daily activities to patient hospitalization. Clinicians caring for patients with asthma must balance therapeutic interventions with the unique disease processes in each individual patient. In addition, clinicians must choose among a wide range of diagnostic tools including highly invasive bronchoalveolar lavage or induced sputum to the noninvasive yet highly involved and patient variable measurements of spirometry and peak flow. Proper management of asthma begins with the monitoring of disease processes in order to enable early intervention. Studies continue to investigate methods that enable the early identification of worsening disease in order to avoid the significant morbidity and mortality associated with asthmatic exacerbations. We have compiled a review of selected articles published in the past 18 months that address new developments in the monitoring of asthma.

## Search strategy

A search of the literature was carried out using PubMed, Ovid, and Embase. Keywords included asthma\*, Monitor\*, and Measur\*. Results were limited to the

English language, human studies, and publication within the past 18 months. Abstracts were selected and reviewed by each author independently. Any disagreement was taken to a third party for further discussion. Articles were organized according to method of asthma monitoring.

## Exhaled nitric oxide

Researchers have sought biomarkers that may assist in either the diagnosis, treatment, or determining the prognosis of asthma. Previous investigations have demonstrated that eosinophilic inflammation, as indicated through induced sputum, can be used to predict corticosteroid response [1]. Fractional exhalation of nitric oxide (F<sub>E</sub>NO) has been studied for a number of years as a potential marker of asthma due to its correlation with airway eosinophilia, and potential to direct future clinical management [2]. An editorial by Pavord and Martin [3] provides a summary of the current literature regarding F<sub>E</sub>NO as a possible diagnostic tool for asthma and the potential to influence the use of inhaled corticosteroids (ICS). Hewitt *et al.* [4<sup>•</sup>] looked at the ability of F<sub>E</sub>NO to direct ICS adjustments in asthma. The number of uncontrolled asthma patients and the dose of ICS were both significantly reduced when directed by F<sub>E</sub>NO [4<sup>•</sup>]. With no control group clinical significance is difficult to ascertain, and further research will be required to determine how much of the effect may be due to increased patient contact and surveillance. An article by Tsuburai *et al.* [5]

also tried to study the cost-effectiveness of bagged F<sub>E</sub>NO for monitoring changes in airway hyper-reactivity following ICS treatment. Forced expiratory volume over 1 s (FEV<sub>1</sub>) did not change significantly, but F<sub>E</sub>NO fell over the treatment period and F<sub>E</sub>NO was found to be a good predictor of improvements in airway hyper-reactivity [5].

### F<sub>E</sub>NO and current treatment guidelines

Guideline-recommended clinical assessments and treatment algorithms currently direct therapeutic interventions in asthma. A study by Szeffler *et al.* [6] investigated if the addition of F<sub>E</sub>NO to current guidelines would reduce over-treatment or under-treatment of asthma and improve overall control. F<sub>E</sub>NO resulted in higher usage of ICS and more frequent use of long-acting B<sub>1</sub> agonists; however, medication reduction with stable clinical indices was not studied [6]. Further investigations might help to determine the clinical usefulness of F<sub>E</sub>NO monitoring and its utility in particular sub-groups (i.e. obese and atopy).

### Reviewing F<sub>E</sub>NO measurement

A literature review by Rodway *et al.* [7<sup>•</sup>] summarized and critiqued various conclusions regarding the utility of F<sub>E</sub>NO and asthma. They address F<sub>E</sub>NO measurements prior to diagnosis, associated decreases with ICS, as well as correlations with sputum eosinophil counts, and airway inflammation [7<sup>•</sup>]. Additionally, they highlighted the need for further research in the clinical implementation of F<sub>E</sub>NO in directing therapies, its role as a marker of inflammation, the use of on-line vs. offline analyzers, and airway-specific sampling to differentiate peripheral lung inflammation [7<sup>•</sup>]. The second review article by Barnes *et al.* [8<sup>•</sup>] provides a detailed background of the physiology behind nitric oxide production, nitric oxide excretion, and the correlation between nitric oxide and asthma as well as other disease states. The authors also provide a detailed background regarding the state of clinical trials involving F<sub>E</sub>NO as well as a number of suggestions to help address various confounding variables and study biases [8<sup>•</sup>].

### F<sub>E</sub>NO collection and measurement

Schiller *et al.* [9] compared a conventional chemiluminescence nitric oxide analyzer with a hand-held device and offline F<sub>E</sub>NO analyzer. The study concluded that F<sub>E</sub>NO measured by chemiluminescence, Niox mino system, and offline methods demonstrated excellent overall correlation [9]. Korn *et al.* [10] compared five F<sub>E</sub>NO analyzers and their ability to return reproducible results. The authors concluded that two analyzers (Medisoft and EcoMedics) had the greatest differences in absolute nitric oxide, whereas the three analyzers by Noix had an acceptable level of agreement though clinical relevance is not defined [10]. Finally, Sonnappa *et al.* [11] compared variation of F<sub>E</sub>NO levels in children

from two different analyzers in comparison to an adult population. The authors concluded that inhaling zero-nitric oxide air prior to analysis by some instruments may not deliver reproducible results and therefore should not be used when measuring F<sub>E</sub>NO in young children [11].

### Combined F<sub>E</sub>NO and pulmonary function

Jackson *et al.* [12<sup>•</sup>] and Chawes *et al.* [13] examined the relationship between F<sub>E</sub>NO, allergic markers, development of recurrent wheeze, and lung function in neonates who had a parental history of asthma. The authors found that F<sub>E</sub>NO was significantly associated with atopy, in particular, children with asthma, allergic sensitization and atopic dermatitis, but was not associated with forced expiratory volume (FEV) or FEV<sub>1</sub>/forced vital capacity (FVC) (forced expiratory volume over one second, functional residual capacity, respectively) [12<sup>•</sup>]. Additionally, Chawes *et al.* [13] concluded that elevated F<sub>E</sub>NO was significantly associated with the development of recurrent wheeze in the first year of life but not thereafter. Munnik *et al.* [14] examined the diagnostic role of F<sub>E</sub>NO compared with a histamine provocation test and FEV<sub>1</sub> reversibility of new referrals to pulmonary outpatient clinics. The authors concluded that F<sub>E</sub>NO, FEV<sub>1</sub> reversibility, and PC<sub>20</sub> can all equally well discriminate asthma from nonasthma (allowing F<sub>E</sub>NO correction of various modifiers, which was not clarified in the article) [14]. Pifferi *et al.* [15] found that combining pulmonary function tests and F<sub>E</sub>NO leads to successful identification of partially controlled asthmatic patients. A study by Graveland *et al.* [16] measured F<sub>E</sub>NO levels in children in correlation with short-term changes of outdoor particulate matter and long-term traffic exposure. The authors found short-term changes in ambient particulate matter were associated with increased F<sub>E</sub>NO, pointing to the possibility that environmental changes can impact F<sub>E</sub>NO levels in the short term [16].

### Miscellaneous F<sub>E</sub>NO studies

Liu *et al.* [17] investigated the ability of F<sub>E</sub>NO and exhaled breath condensates (EBC) pH to measure the level of airway inflammation and thereby adjust the levels of inhaled corticosteroids. Though it was a very small study they found weaning ICS caused a rise in F<sub>E</sub>NO and a drop in pH, which correlated with an impending exacerbation [17]. Other laboratories looked at the addition of different medications and the relationship with F<sub>E</sub>NO. Gelb *et al.* [18] presents a nonrandomized, nonplacebo single-blinded pilot study of stable asthmatic patients and investigated the role of a leukotriene synthesis inhibitor, zileuton. After 4 weeks there was no significant difference in F<sub>E</sub>NO and Juniper airway scores, though a significant, but small, improvement in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC was noted [18]. The impact of sildenafil on F<sub>E</sub>NO was investigated by Rothe *et al.* [19] in a small randomized crossover placebo-controlled study of 10

male nonasthmatic individuals. The authors found that a single dose of sildenafil did not significantly raise  $F_{E}NO$ .

### Exhaled gases

A meta-analysis [20] of 15 randomized control trials from 1997 to 2008 revealed asthmatic patients have significantly higher levels of exhaled carbon monoxide (eCO), a greater expression of hemoxygenase-1, and a correlation of eCO with steroid therapy. The arterial partial pressure of  $CO_2$  ( $PaCO_2$ ) is predictive of the need for ventilation, ICU admission, and mortality. However, arterial blood gases are highly invasive with certain risks associated with their placement. Perrin *et al.* [21] recruited patients with either severe asthma or suspected pneumonia and investigated if transthecal carbon dioxide ( $PtCO_2$ ) monitors correlated with  $PaCO_2$ . The authors concluded that  $PtCO_2$  could accurately assess  $PaCO_2$ . Further clinical trials may help to determine if these devices may help direct asthma therapy in the acutely ill [21].

### Pulmonary function

Several studies were published that reviewed current pulmonary function techniques and the ability to accurately monitor asthma. Mishima [22] reviewed the differences in spirometry between asthma and chronic obstructive pulmonary disease (COPD) and highlighted the important parameters that distinguish asthma from other pulmonary diseases. The authors also suggested additional methods that might help differentiate asthma from COPD that include impedance, resistance and reactivity [23]. Desalu *et al.* [24] performed a cross-sectional survey of Nigerian doctors regarding spirometry and found most are aware of spirometry, but a lack of access to equipment is a major barrier to usage. Scichilone *et al.* [25] reviewed the literature concerning spirometry parameters as well as high-resolution computerized tomography (CT) scans in the diagnosis and monitoring of asthma. The authors concluded that the utility of spirometry in conjunction with high-resolution CT in asthma monitoring remains to be determined [25]. A cross-sectional study by Kalhoff *et al.* [26] recruited children during medical check-ups in an effort to update child reference values for spirometry. The authors found that current reference values largely overestimate maximal flow rates of preschool children, as well as a nonsignificant trend of  $FEV_1$  and FVC with increasing body mass index (BMI) [26]. A study by Janson *et al.* [27\*\*] recruited adults with persistent asthma and found that during high-risk season peak flow meter monitoring improved asthma control, and patients had an improved perception of their disease state. A small study by Purokivi *et al.* [28] recruited steroid naïve asthmatic and nonasthmatic patients and found that the ratio of coughs due to histamine concentration decreased over time with ICS treatment in

the asthmatic patients. A study by McCoy *et al.* [29] determined there was no difference between standing and sitting when providing peak expiratory flow (PEF) measurements. A systematic review by Callahan *et al.* [30] presented randomized control trials of symptom-based management with or without PEF and found no difference in any outcomes. Some studies had conflicting results about the correlation of PEF with deteriorating asthma control and  $FEV_1$ , pointing to the need for large-scale studies regarding PEF usage as a management tool for pediatric patients with asthma. Grad *et al.* [31] studied internet-based self-monitoring of symptoms and PEF in a school setting for pediatric asthma control. Authors noted that PEF readings are feasible and qualitatively appeared to track disease and symptoms, but symptom-based interventions may be more time and cost-effective. Monitoring changes in PEF as the mean, coefficient of variation, or autocorrelation and its predictive power for loss of asthma control following withdrawal of ICS was studied by Thamrin *et al.* [32\*\*]. Mild to moderate asthma patients provided PEF data over a 6-week follow-up and found that mean and coefficient of variation of PEF changes were correlated to loss of control. They also found that  $F_{E}NO$  had similar sensitivity for predicting loss of control within the first 2 weeks of ICS withdrawal [32\*\*]. Oga *et al.* [33] attempted to find ancillary measurements that may compliment  $FEV_1$  values in asthma and COPD. The authors could not find support for including anxiety, dyspnea, or the Saint George Respiratory Questionnaire into asthma measurements, but acknowledge additional work is needed [33]. Halimi *et al.* [34] studied personality and social traits in asthmatic patients in order to predict poor adherence to therapy. Along with peak flow monitoring the authors found that young age, hospital admission, nocturnal awakenings, extraversion, and an external locus of control were associated with poor therapy adherence [34]. Henderson and Ahern [35] investigated the contribution of serial PEF during emergency department (ED) visits for acute exacerbation through a prospective institutional review study of mild to moderate asthmatic patients. The study found no correlation between outcome (admission or discharge) and PEF% of predicted; as well, improvement in PEF seen after the first ED inhaled therapy described 86% of the total improvement [35]. Another study of asthma in the ED by Nik Hisamuddin *et al.* [36] looked at correlations between capnographic waveforms and PEF. The study found that capnography did not correlate with PEF, but may have some benefits as effort independent and allows more continuous monitoring [36].

### Questionnaire/self-assessment

Continuing research is attempting to clarify the utility of periodic reviews of symptoms and indicators of asthma control in order to better control symptoms and limit

exacerbations. O'Connor *et al.* [37] reviewed insurance claims from 2001 to 2004 and found that the risk of exacerbations was greatest in patients with a history of both sub-acute lack of asthma control and exacerbations. The authors found that subacute lack of asthma control and a history of exacerbations are independent predictors of future exacerbations [37]. Another study by Burgess *et al.* [38] followed children for 4 months looking at the level of adherence and medication usage in children with unstable asthma by using an electronic monitoring device. The authors found a significantly higher rate of medication adherence and a greater improvement in FEV<sub>1</sub> and propose a possible role for electronic monitoring devices in asthma management [38]. Jiang *et al.* [39] followed patients with symptomatic asthma using a fixed-time electronic or paper assessment schedule for 2 weeks. The authors believe the electronic devices produced better compliance with data entry, but was impacted by convenience, user-friendly electronic devices and whether it was found to be less disruptive to patients' daily life [39]. Moderate-severe to severe asthma patients were recruited in a study by Liu *et al.* [40] investigating the utility of a cell phone-based self-care system. PEF was increased, quality-of-life measures were improved, exacerbations were fewer and unscheduled hospital visits were fewer in the patients receiving cell phone-based self-care system [40]. Paré *et al.* [41] reviewed publications from 1966 to 2008 examining the clinical effects associated with telemonitoring. A review [41] of 62 studies found an increase in peak flow, a decrease in disease severity, and an increased quality of life with home telemonitoring. Prabhakaran *et al.* [42] investigated the use of text messaging questions to patients about their symptoms and medication adjustment and found an insignificant reduction in ED visits and nebulizations compared with control individuals. Van der Meer *et al.* [43] recruited adults with mild to moderate persistent asthma to a 1-year randomized trial of weekly self-monitoring using the internet for standard care versus those receiving usual care. The authors found that initially the internet-based group had improved control without significant increase in pharmacological intervention, but at the study's end both groups had similar asthma control [43]. A randomized control study by Jacobson *et al.* [44] recruited children using either electronic or paper-based diaries and found no statistically significant difference in the number of ED visits or hospitalizations (even though the paper-based group had fewer logged days). Sarria *et al.* [45] present a Portuguese translation of the pediatric asthma quality-of-life questionnaire and attempt to validate its use among asthmatic children. They attempt to investigate the psychometric properties of the survey and feel that they are able to reproduce the validity of its use in their Brazilian population. Finally, LØdrup *et al.* [46] offer a guide for problematic severe pediatric asthma patients by leading you through a full diagnostic work-up, multidisciplinary assess-

ment, measurements of inflammation, as well as steroid responsiveness. As well, following each category of the work-up the authors summarize important research gaps that need to be addressed [46].

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## Guidelines

Bousquet *et al.* [47] outline an internationally standardized definition of severe and uncontrolled asthma as presented to the World Health Organization Consultation on Severe Asthma. A summary of the latest expert panel consensus for primary care of asthma was presented by Pollart and Elward [48]. The Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program (NAEPP) was based upon the Guidelines for the Diagnosis and Management of Asthma released in 1997. The new guidelines focus on asthma evaluation to determine appropriate treatments based upon current impairment, severity, control, and future risk of decompensation [48]. Kwong *et al.* [49] present a retrospective analysis of inner city children with asthma who underwent a stepwise reduction of their asthma controllers based upon NAEPP and EPR-3 guidelines. This article found that cessation of asthma controller medication resulted in loss of asthma control in a significant number of patients, and found that clinical monitoring was important in order to reduce impairment due to loss of asthma control [49]. The effectiveness of school-based asthma management was studied by Maa *et al.* [50] who found that FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC ratios all improved up to 12 months, but at the 18-month assessment only FEV<sub>1</sub> showed significant improvement. The study was quite small, but points to the possibility of public health monitoring, asthma teaching, and monitoring in schools.

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## Reviews

The latest evidence-based literature for directing inhaled corticosteroids in asthma patients was reviewed by Fromer [51] in a recent article. Another review article by Petsky *et al.* [52] looked at two adult and four children studies surrounding F<sub>E</sub>NO for adjusting asthma therapy. Diamant *et al.* [53] provides a review of several different sampling techniques of asthma biomarkers, the associated advantages and disadvantages, and possible clinical use. Nair and Hargreave [54] authored a review of literature investigating the utility of spontaneous or induced sputum with F<sub>E</sub>NO as clinical tools for the monitoring and guidance of therapeutics in asthma. Finally, To *et al.* [55] performed a systematic literature review in order to develop performance indicators regarding the quality of primary care of asthma. The authors propose 15 indicators as possible benchmarks through which to measure optimal healthcare delivery to asthma patients [55].

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## Surveillance

Two articles published in the past 18 months addressed methods of surveillance for monitoring asthma prevalence and control in the greater community. A study by Tokars *et al.* [56] provided a systematic summary of data collected by the Centre for Disease Control (CDC) BioSense program which automatically collects and processes data from various federal partners, health departments, and hospitals in order to allow the monitoring and response to emergencies for public health departments. Another data mining program incorporating biosignal and environmental data is described by Lee *et al.* [57] and demonstrates two methods, Pattern Based Decision Tree (PBDT) and Pattern Based Class-Association Rule (PBCAR), for asthma monitoring. Both articles highlight methods through which researchers or public health departments can monitor population-based asthma patterns.

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## Condensate

Lázár *et al.* [58] utilized a cross-sectional study to define a possible relationship between adenosine triphosphate (ATP) in the exhaled breath condensate (EBC) and different asthma markers. Participants underwent EBC collection, F<sub>E</sub>NO, spirometry, and asthma control test (ACT) scores. The authors found no difference in ATP concentrations in EBC from asthma and control individuals. As well, there was no correlation between EBC-derived ATP concentrations and bronchoconstriction, F<sub>E</sub>NO, or ACT scores [58].

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## Saliva

Two studies published in the past 18 months used saliva as a tool to monitor asthma. In a cross-sectional study of asthmatic patients with concurrent allergic rhinitis and atopic dermatitis Koh *et al.* [59] measured whole saliva and serum eosinophilic cationic protein (ECP) as well as reactivity skin prick tests. The authors found no association of salivary ECP with severity, atopy conditions, medication use, skin prick test results, or serum ECP [59]. A study by Watanabe *et al.* [60] attempted to assess the relationship between a declining night-time salivary pH and airway hyper-responsiveness in mild asthmatic patients. The authors found that a greater change in pH during the night correlated with greater airway hyper-responsiveness.

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## Sputum

A study by Nair and Hargreave [54] reviewed current methods and three clinical cases for the use of sputum analysis to direct the treatment of patients with airway inflammation. Reference tables of normal values and possible treatment protocols that may be of use in the

future are also presented. Chakir *et al.* [61] followed asthmatic patients treated for 2 years, guided by either clinical criteria or sputum eosinophil counts. The authors found that clinically guided therapeutics resulted in reduced eosinophil and neutrophil counts, whereas the sputum group showed reduced lymphocyte and eosinophil counts but neutrophils were unaffected [61]. Amorim *et al.* [62] designed a cross-sectional study comparing eosinophil counts in induced sputum to nasal lavage in adult asthma patients. The authors found an association of nasal eosinophils with sputum eosinophil counts but no association of nasal eosinophils with FEV<sub>1</sub>, pre/post-bronchodilator FEV<sub>1</sub>, or ACQ scores [62].

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## Miscellaneous

A number of studies have begun to expand the traditional scope of asthma monitoring to intriguing avenues. Shedeed [63] recruited control and asthmatic children and followed for 1 year and demonstrated that asthma patients had thicker right ventricular walls, an impaired relaxation pattern and impaired diastolic function. Mild asthmatic patients without any clinical symptoms demonstrated lower systolic volumes [63]. Another article by Pereira-Vega *et al.* [64] attempted to identify a relation between premenstrual symptoms and asthma. The authors noted abdominal tension and mammary tensions were increased in women with premenstrual asthma and dysphoric-psychiatric symptoms had a clear link with premenstrual asthma [64].

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## Conclusion

Over the past year most publications have focused on biomarkers (F<sub>E</sub>NO, CO<sub>2</sub>, saliva, EBC, sputum) and their use in monitoring asthma. F<sub>E</sub>NO analysis in particular is relatively cheap, simple, and delivers a numerical reading very rapidly which could assist in the decision of appropriate therapeutic interventions. Although biomarkers offer a promising noninvasive method more detailed studies and validations are still required before most can be incorporated into standard monitoring techniques. Refinement of current pulmonary function testing and clinical guidelines concerning lung function measurement will allow more accurate monitoring of asthma in children considered to be at high risk for exacerbation. Increased self-monitoring through electronic communication has also demonstrated a net improvement in the stability of asthma in patients. Overall this past year has provided important improvements to our current knowledge base in the field of asthma monitoring.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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