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# Assessing clinical and spirometric control and the intensity of the inflammatory process in asthma

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**Abstract**

**Objectives:** To review the role of clinical assessment, quality of life assessment, spirometry, bronchial responsiveness test and inflammatory markers for asthma assessment.

**Sources:** Search run on MEDLINE and LILACS.

**Summary of the findings:** Clinical assessment aids with assessing asthma control and is widely recommended. However, patients may have airway inflammation and obstruction despite normal clinical findings. Spirometry quantifies the degree of airway obstruction and helps with diagnosis, while the bronchial responsiveness test may be indicated for when asthma is suspected but spirometry is normal. The results of assaying the inflammatory markers in exhaled breath condensate, induced sputum, bronchoalveolar lavage and bronchial biopsy specimens are abnormal in asthma patients, but these are complex techniques almost always restricted to research. Fractional exhaled nitric oxide (FeNO) is elevated in patients with asthma, is reproducible and noninvasive and reduces with treatment. Studies have investigated using FeNO to help with adjusting inhaled corticoid dosages, but the benefits are not clear.

**Conclusions:** A range of different methods are needed to accurately assess disease control, all with their advantages and limitations. Clinical and functional assessment is useful for diagnosing asthma, but is of limited use for precisely evaluating the intensity of the inflammatory process in the airways. More randomized and controlled studies with adequate statistical power should be carried out to investigate the true utility of noninvasive inflammatory markers, especially FeNO, for asthma management.

*J Pediatr (Rio J). 2010;86(2):93-100:* Asthma, inflammation, quality of life, bronchial hyperresponsiveness, nitric oxide, spirometry, exhaled breath condensate, induced sputum.

## Introduction

Evaluation of asthma control is still a challenge for clinicians. Once the disease has been diagnosed and classified, it is the physician's responsibility to select the appropriate treatment for the severity of the case and periodically evaluate the patient in order to determine their asthma control level.[1] Asthma management guidelines recommend clinical and functional assessment for evaluating control.[1-4] Quality of life questionnaires can also be administered in order to further refine the impact of the disease and the patient's treatment.[1]

The limitations of clinical and functional parameters for precisely identifying the intensity of the inflammatory

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process in the airways has meant that, in recent years, the use of inflammatory markers,[5-7] and of fractional exhaled nitric oxide (FeNO) in particular,[7] has attracted a great deal of research interest.

When combined with clinical status and spirometry, inflammatory markers play a role in monitoring the inflammatory process and, as a result, facilitate patient management and disease control.

Airway inflammation can be assessed using the bronchial responsiveness test, inflammatory markers from exhaled breath condensate, analysis of cellularity and mediators in induced sputum or bronchoalveolar lavage and even on the basis of the inflammatory profile of bronchial biopsy specimens. Nevertheless, the majority of these markers require invasive procedures, do not provide instant results and many of them demand great care with sample storage and analysis. Furthermore, they may temporarily compromise patients' clinical status. For these reasons they have limited clinical applicability and the majority of them are restricted to the sphere of research.

In contrast, FeNO is measured noninvasively, is well-tolerated, is reproducible and offers immediate results.[7] Fractional exhaled nitric oxide levels are elevated in asthma[8-11] and reduce after treatment with corticoids[12] and are considered a sign of the "inflammometry era" of asthma management.

The objective of this review article is to present, review and discuss the role of clinical and functional assessment; quality of life questionnaires and inflammatory markers, with emphasis on FeNO, on asthma diagnosis and assessment of asthma control level and on the intensity of the inflammatory process.

Therefore, a narrative literature review was carried out using the MEDLINE and LILACS databases to search for publications from the last 15 years with the following search terms: asthma, airway inflammation, quality of life, bronchial responsiveness, nitric oxide, lung function, biomarkers, exhaled breath condensate, induced sputum and noninvasive monitoring.

## Clinical assessment and quality of life

The majority of consensus statements on asthma recommend that during the medical consultation daytime, nighttime and awakening symptoms, reliever medication use and limitations to activities should be assessed to estimate the level of asthma control.[1-4] It is also known that uncontrolled asthma is associated with a deterioration in quality of life and increased utilization of health services, unscheduled consultations, emergency room visits and hospitalizations.[2] It is not difficult to obtain these data in clinical practice; however, clinicians should be alert to the possibility that the absence of these symptoms does not guarantee that spirometry has normalized nor that the airways have no inflammation. For example, Jentzsch et al.[13] assessed 35 children and adolescents with persistent asthma and found elevated FeNO levels in patients who appeared healthy according to clinical examination and spirometry.

Another method that can aid in assessing the extent to which asthma is compromising patients' daily lives is administration of quality of life questionnaires. Unfortunately, the available arsenal of questionnaires validated for the pediatric population is smaller than that available for the adult population. The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) proposed by Juniper et al. is the instrument that has been most studied.[14] It has been validated for the Portuguese spoken in Brazil and is applicable to children from 6 years of age onwards. The PAQLQ is self-administered and comprises 23 items. It quantifies the degree of compromise caused by asthma on a scale of 1 to 7 points per item, with 1 indicating maximum compromise, and 7 points no compromise. The points for each item are summed and then divide by 23. Final scores of less than 4 indicate compromised quality of life.

While quality of life questionnaires are recognizedly useful for assessing the impact of the disease on patients' lives, they are unfortunately underutilized in clinical practice, and are basically restricted to use in research. Furthermore, there may be a disparity between the parameters proposed by guidelines and those used in the questionnaires, since patients may be controlled according to the parameters recommended by the guidelines, but still exhibit compromised quality of life, and vice-versa.[15,16] For example, Alvim et al. found a relatively high mean PAQLQ score (5.7±1.3) for 146 adolescents from public schools suffering from asthma of varying degrees of severity.[15] In turn, Ehrs et al. observed low correlation coefficients (r) for quality of life questionnaires against FeNO, spirometry and the bronchial responsiveness test, varying from -0.07 to 0.13 [95% confidence interval (95%IC) -0.3 to 0.3].[16]

There is another, shorter, questionnaire available for clinical use. This is the Asthma Control Test, ACT, which is simpler to administrate than the PAQLQ because it only comprises five questions with five possible answers for each.[17] This has not yet been validated for Brazil however, and has only been studied with patients over the age of 18, which, for now, prevents its use in pediatrics.

## Functional assessment

### *Spirometry*

Spirometry is widely recommended by national and international guidelines on asthma management and makes it possible to objectively identify airway obstruction, which may be underestimated by patients.[1-4] An increase of 12% or more in forced expiratory volume in 1 second ($FEV_1$)

after bronchodilation confirms a diagnosis of asthma.[1-4] It is possible to measure $FEV_1$ in children from 6 years of age onwards, it is reproducible and, depending on the severity and duration of the disease, may return to normal.

In common with the PAQLQ, spirometry does not have an elevated coefficient of correlation with methods that identify the intensity of airway inflammation. Therefore, the absence of obstructive ventilatory disorders does not necessarily indicate an absence of inflammation. Paro-Heitor et al.[18] studied the behavior of FeNO compared with spirometry in a study following 26 asthmatic children treated with inhaled corticoids (IC). The authors did not observe significant correlations between FeNO and $FEV_1$ in any of three assessments over the 3 months of follow-up ($r = 0.297$, $p = 0.141$; $r = -0.06$, $p = 0.759$; and $r = 0.260$, $p = 0.243$, respectively). According to these authors, functional stability or an absence of obstruction detected by spirometry may not indicate adequate control of the disease, whereas serial FeNO measurements appear to reflect the anti-inflammatory effect of these medications more satisfactorily.

### *Bronchial responsiveness test*

Another useful test for diagnosing asthma is the bronchial responsiveness test, since it assesses the degree of bronchial hyperresponsiveness,[1,19] which is a characteristic of asthma. It is indicated for patients with a clinical suspicion of asthma, but normal spirometry.[1] It offers more than 95% sensitivity,[20,21] but has moderate or low specificity, since patients with other diseases such as cystic fibrosis, allergic rhinitis and bronchiectasis may also have abnormal bronchial responsiveness test results.[1] This test can be used for patient follow-up, especially in studies evaluating long-term responses to asthma treatment.[22,23] It is known that an absence of airway inflammation leads to a reduction in symptoms and normalization of bronchial hyperresponsiveness[24] and that when patients are treated with IC, their bronchial hyperresponsiveness reduces.[25,26] Despite this, incorporation of the bronchial responsiveness test into management of patients with asthma is not yet widespread, particularly within the pediatric age group. Nuijsink et al. found that guiding asthma treatment by bronchial responsiveness test results did not lead to benefits in terms of number of days without symptoms, but did improve $FEV_1$ in 210 children with asthma followed for 2 years.[27]

Notwithstanding, the bronchial responsiveness test also suffers from certain limitations, such as its increased cost when compared with spirometry, the greater time required and, finally, the increased risk of temporarily worsening airway obstruction.[19] Bronchial responsiveness tests should therefore be carried out under appropriate conditions and by trained professionals.

### *Diurnal variability of peak expiratory flow (PEF)*

Peak expiratory flow variability is expressed as a percentage and is the difference between the highest and the lowest flow results tested in the morning and at night for 2 to 3 weeks. According to the Global Initiative for Asthma (GINA), variability greater than 20% is suggestive of a diagnosis of asthma,[1] although this recommendation has been questioned by other guidelines.[2,28]

The most attractive features of PEF diurnal variability are its ease of application, lower cost than other methods and accessibility to pediatricians. Despite these advantages, PEF can underestimate the degree of airway obstruction when compared with $FEV_1$.[29] Eid et al. investigated 244 asthma patients aged 4 to 18 years and with varying levels of severity, finding that 30% of patients with normal PEF had abnormal spirometry.[29] Furthermore, since the measurement is effort-dependent, patients must be properly instructed and the quality of each measurement should be verified.

According to both GINA and to national guidelines, PEF diurnal variability of less than 20% is one of the criteria for classifying asthma as intermittent, while variability of 20 to 30% and greater than 30% correspond to persistent mild and persistent moderate-severe asthma, respectively.[1,4] With relation to the criteria for disease control level, the same guidelines suggest that a PEF that is 80% or more of expected can be considered normal or near-normal.[1,4]

## Inflammatory markers

Since asthma is a chronic inflammatory disease, in recent years attention has turned to the search for noninvasive, safe and easily-obtained methods that can identify and quantify the intensity of the inflammatory process in the airways. Such methods include testing for inflammatory markers in induced sputum or exhaled breath condensate and FeNO measurements.

### *Induced sputum*

Evaluation of inducing sputum obtained with hypertonic saline solution provides information on the inflammatory events of asthma. Studies have detected elevated eosinophil counts and eosinophilic cationic protein concentrations (which are related to eosinophil activity) in the induced sputum of asthmatic patients.[5]

One Brazilian study investigated inflammatory markers in induced sputum from 96 asthma patients aged 6 to 18 years.[30] The collection rate in that study was 70.8% and, for their sample, collecting sputum proved to be safe and free from adverse clinical effects. Nevertheless, eosinophil counts did not indicate clinical or functional severity since 60% of clinically stable patients on IC still had a percentage of eosinophils in sputum greater than 2.5%. Furthermore,

there was no correlation between eosinophil counts in sputum and spirometry (r = 0.118, p = 0.336), which suggests that an absence of airway obstruction does not necessarily mean that inflammation is under control.

### *Exhaled breath condensate*

This method offers noninvasive collection of several different non-volatile molecules from the respiratory tract, such as adenosine, ammonia, hydrogen peroxide, isoprostanes, leukotrienes, cytokines, peptides and a variety of ions. Patients with asthma have abnormal results, when compared with healthy controls.[6] It is known that the addition of this sample collection technique opens up a promising field of research, but there are currently many unanswered questions about the role these molecules play in the pathophysiology of asthma and about the applicability of exhaled breath condensate to clinical practice.

### *Bronchoalveolar lavage and bronchial biopsy*

There are few studies analyzing specimens obtained by bronchial biopsy or by bronchoalveolar lavage from children with asthma. These procedures are restricted to research that aims to investigate remodeling and inflammation of the airways. Hypertrophy of the peribronchial musculature, eosinophilic inflammation and epithelium loss can all be observed in schoolchildren with asthma.[31] Studies indicate that eosinophilic infiltration comes first, followed by remodeling, which may lead to progressive obstruction of airflow.[31] Notwithstanding, bronchoalveolar lavage and bronchial biopsy are invasive and, therefore, are not indicated for routine assessment of patients with asthma.

### *Fractional exhaled nitric oxide (FeNO)*

Fractional exhaled nitric oxide is a noninvasive marker that has attracted a great deal of interest from scholars. It is not invasive, offers immediate results, is elevated in patients with asthma,[6,12] but reduces with treatment,[5] is well-tolerated by patients and correlates with eosinophilic inflammation.

Nitric oxide is synthesized by three enzymes, the nitric oxide synthases, which are present in many organs, including the lungs, nostrils and paranasal sinuses.[12,32,33] Inducible nitric oxide synthase (iNOS) is induced in many types of cell by exposure to proinflammatory cytokines and endotoxins. In the airways, nitric oxide has a bactericidal action and is active in ciliary movement in addition to provoking bronchodilation and vasodilation.[34]

### *Measurement methods*

A constant expiratory flow of around 50 mL/second and expiration against a pressure of 5 - 20 $cmH_20$ without nose clips are necessary for measuring FeNO.[7]

The reaction between NO and ozone can be used to measure FeNO by chemiluminescence, counting the number of photons emitted as the NO molecules return to their normal state. In 2005, portable NO analyzers became available, measuring FeNO using an electrochemical method rather than chemiluminescence and making the test simple and portable.

### *Reference values for FeNO*

Buchvald et al. carried out a multicenter study of 405 healthy children and adolescents aged 4 to 17 years in order to determine normal FeNO levels for this age group.[35] The geometric mean was 9.7 ppb, and the upper limit was 25.2 ppb, with no difference between sexes.

### *Assessing the intensity of the inflammatory process in asthma*

In common with adults, children and adolescents with asthma have elevated FeNO levels.[8-11] Byrnes et al. found that 15 children with asthma had FeNO levels that were approximately 3 times higher than 39 healthy children.[9] There is evidence that this difference is related to the increased expression of iNOS in the respiratory epithelium cells of asthmatic patients.[36]

Fractional exhaled nitric oxide levels reflect the intensity of eosinophilic inflammation, which is characteristic of asthma, since they correlate with other inflammatory markers such as increased eosinophils in the bloodstream, sputum and bronchial mucosa.[7,36,37] Jatakanon et al. found a significant correlation (r = 0.48) between FeNO and the percentage of eosinophils in induced sputum from 35 patients with asthma.[37] Furthermore, FeNO correlates with bronchial hyperresponsiveness (r = -0.64),[37] bronchodilator reversibility and atopic disease.[7,10,13] Jentzsch et al.[13] assessed 45 children and adolescents with persistent asthma and found that FeNO was higher in asthmatics (16.7 ppb) than non-asthmatics (5.3 ppb; $p < 0.01$). Of note in that study were the elevated FeNO levels observed in patients with normal clinical and spirometric findings. Kovesi et al. observed similar results in a sample of 1,135 schoolchildren.[10] Children who had asthma and reported atopic disease had a mean FeNO of 22.8±23.6 ppb, while children with asthma but without atopic disease had mean FeNO of 15.8±15.6 ppb, $p < 0.01$.

### *Clinical applications of FeNO in children and adolescents with asthma*

*Diagnosis*

Smith et al. examined 47 children and adults who had been referred for diagnostic assessment with symptoms suggestive of asthma and found that FeNO had better diagnostic accuracy than spirometry or peak expiratory

flow.[38] Patients were assessed three times at two-week intervals. Asthma was diagnosed at the last consultation on the basis of clinical history according to the American Thoracic Society (ATS) criteria and a positive bronchial responsiveness test result and/or a positive bronchodilatory response characterized by an increase in $FEV_1$ greater than or equal to 12%. The sensitivities of diurnal PEF variation and increase in $FEV_1$ after a course of corticoid vary from 0 to 47%, whereas FeNO over 20 ppb had sensitivity and specificity of 88 and 79%, respectively.

Still on the subject of the application of FeNO to diagnostic investigations, Malmberg et al. showed that FeNO was better than spirometric parameters for identifying children with suspected asthma.[39]

*Inhaled corticoids and FeNO levels*

One of the reasons why FeNO has provoked growing interest among researchers is the fact that IC inhibit the expression of the nitric oxide synthases, and as a consequence they also reduce FeNO concentrations. Table 1 lists studies that reported the behavior of FeNO levels and the medications used for asthma control.

Table 1 shows that the majority of studies with children have small samples, but the authors consistently recorded reductions of around 40% in FeNO in patients treated with medications for a minimum of 2 weeks.[40-43] Szefler et al.[43] conducted a study of 546 patients aged from 12 to 20 years, followed for 46 weeks and treated with fluticasone at dosages varying from 100 to 500 mcg per day and with a combination of fluticasone with salmeterol at dosages varying from 100/50 to 500/50 mcg per day. At admission these patients had a mean FeNO of 31.7 ppb (14.1 to 64.4). The median reduction in FeNO was 20.1 ppb and the mean of 12.9 ppb corresponds to a reduction of approximately 41%. In the majority of studies that used IC, FeNO values were observed to return to normal.

*Predicting asthma worsening after withdrawing IC*

The accuracy of FeNO for early detection of exacerbations has not yet been defined in comparison with conventional measurements. Notwithstanding, Pijnenburg et al. investigated the utility of FeNO for detecting asthma deterioration after withdrawal of IC in a double-blind randomized study of 40 children. Fractional exhaled nitric oxide was measured 2, 4, 12 and 24 weeks after withdrawal of the IC. Spirometry was also performed and symptoms were recorded. The authors found that a cut off point of 49.0 ppb 4 weeks after withdrawal offered the best combination of sensitivity and specificity for detecting asthma deterioration.[44] Nevertheless, they pointed out that their sample was relatively small and some children had elevated FeNO levels, but their asthma did not deteriorate.

*The role of FeNO as an auxiliary parameter to titrate IC dosage*

Several different studies have been conducted in order to evaluate the utility of FeNO for IC dosage decision-making.[45-48] Table 2 lists some randomized clinical trials in which patients were allocated to one of two groups: the first in which corticoid dosages were adjusted according to asthma guidelines, i.e., according to clinical and functional findings; and a second in which IC increases were based on FeNO levels. The results indicate differences observed in the group managed according to FeNO in relation to the group managed according to the guidelines.

In a double-blind study lasting 12 months, Pijnenburg et al. assessed 85 children who had been on IC for at least 3 months prior to the study, 42 in a group managed according to FeNO + symptoms and 47 in a group managed according to symptoms only.[46] Patients were evaluated every 3 months for clinical score and FeNO. If children in the FeNO group exhibited a low clinical score and FeNO below 30 ppb, then the IC dosage was reduced, and vice-

**Table 1 -** Variations in fractional exhaled nitric oxide levels of asthmatic patients treated with medications used for asthma control

| Authors | n | Corticoid | Duration (weeks) | Variation FeNO (ppb) | Reduction FeNO (%) |
|---|---|---|---|---|---|
| Pedersen et al.[40] | 17 children | Beclomethasone | 12 | 16-8.9 | 44.3 |
| Verini et al.[41] | 12 children | Fluticasone + antileukotriene | 2 | 14-8.5 | 39.3 |
| Montuschi et al.[42] | 14 children | Antileukotriene | 4 | 45-7.9 | 17.0 |
| Szefler et al.[43] | 546 adolescents | Fluticasone, bronchodilator fluticasone + long-acting | 46 | – | 41.0 |

FeNO = fractional exhaled nitric oxide.

versa. Spirometry and bronchial responsiveness tests were performed at the start and end of the study. The primary outcome was the mean IC dose throughout the study. The researchers pointed out that after 12 months the groups did not differ in relation to $FEV_1$ values, clinical scores or IC dosages. However, hyperresponsiveness was lower in the FeNO group than in the control group. In turn, Fritsch et al., investigated a smaller number of patients followed for 6 months and found that the FeNO group was on lower IC dosages at the end of the study.[45]

As can be observed in Table 2, the studies differ in terms of duration, FeNO cutoff points, interventions and outcomes. Furthermore, the definitions of exacerbations are not homogenous. Using FeNO as a parameter for changing patient management appears to offer few advantages over the traditional parameters: clinical findings and pulmonary function. In general in these studies the FeNO-managed group took lower IC doses without compromising disease control. However, there were no statistically significant differences between the groups in terms of the number of exacerbations and number of days without symptoms.

Although it is often used in investigations of asthma patients, the role of FeNO as a parameter for evaluation and management of patients with asthma is not yet clear. The authors of a systematic review for the Cochrane Collaboration concluded that the role of FeNO in choosing IC dosages is not yet well-defined and that more studies are needed.[48]

After that review had been published, two more clinical trials were conducted to assess the utility of FeNO for patient management.[43,49] Szefler et al. conducted a multicenter, double-blind, randomized clinical trial following adolescents aged 12 to 20 years with persistent asthma for 10 months. Both conventional management and management with FeNO offered good control of symptoms. However, the FeNO group took higher dosages of IC without significant improvement of asthma control in relation to the control group.[43] Recently, De Jongste et al. assessed daily FeNO measurements for the management of asthma in atopic children.[49] The 151 patients recruited were randomized into two groups: one used daily home-measured FeNO plus the clinical score, while the other used the clinical score only. Both groups had clinical function improvement and reductions in FeNO and IC dose. There was a tendency to a lower number of exacerbations in the group that used FeNO monitoring. The authors concluded that FeNO did not improve asthma control or increase the reduction in corticoid usage.

## Final comments

Asthma is a complex disease with a wide variability of presentation. This being so, a range of different methods are needed to achieve diagnosis and assess disease control, all with their advantages and limitations. Clinical parameters, quality of life assessment, pulmonary function testing and the methods of inflammometry all assess different aspects of the disease and complement each other.

Studies that will certainly be published in the future will investigate the best way of interpreting all of these features and of understanding correlations between all of the parameters. It is therefore prudent to await such results before incorporating inflammatory markers into routine clinical practice, especially FeNO.

More randomized and controlled studies with adequate statistical power should be carried out to investigate the true utility of noninvasive inflammatory markers, especially FeNO,

**Table 2 -** Randomized clinical trials comparing asthma treatment control based on fractional exhaled nitric oxide with clinical status and spirometry

| Authors | n | Population | Duration (months) | Criteria for increasing inhaled corticoid | Outcomes | Results |
|---|---|---|---|---|---|---|
| Fritsch et al.[45] | 47 | Children and adolescents | 6 | FeNO greater than 20 ppb | Spirometry, exacerbations, IC dosage, bronchodilator usage | Improved spirometry, reduced IC dosage |
| Pijnenburg et al.[46] | 85 | Children and adolescents | 12 | FeNO greater than 30 ppb | Spirometry, bronchial responsiveness test, IC dosage, clinical score, OC use | Reduction in bronchial hyperresponsiveness |
| Smith et al.[47] | 97 | Adolescents and adults | 15-24 | FeNO greater than 35 ppb | Exacerbations, mean daily IC dose | Reduction in IC dosage |

IC = inhaled corticoid; OC = oral corticoid; FeNO = fractional exhaled nitric oxide.

for asthma management. It is possible that, as research advances, FeNO analysis will be incorporated into clinical practice, facilitating patient management.

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