

Improving Diagnosis and Management of Asthma through F_{ENO} Measurement



F_{ENO} – Fractional Exhaled
Nitric Oxide

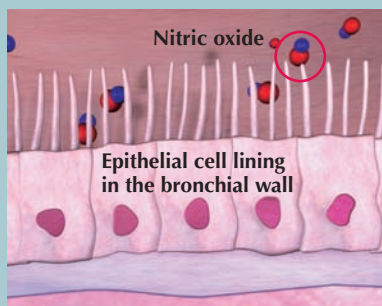
Aerocrine

What is NO?

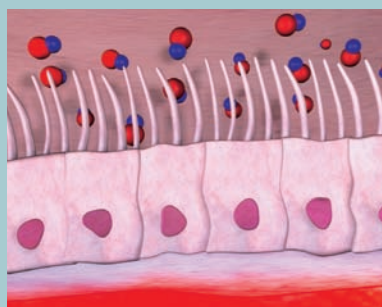
Nitric oxide (NO) is produced in the epithelial cells of the bronchial wall as an intrinsic part of the inflammatory process. NO production has been shown to increase when there is eosinophilic airway inflammation^{1, 2}.

The presence of endogenous NO in exhaled air was first reported in 1991 by Gustafsson et al.³ and in 1993 Alving et al. found that NO in exhaled air was elevated in patients with asthma⁴. Since that time research has been directed at uncovering the role that NO plays in airway inflammation.

There has been a continuous flow of research and a large body of data (nearly 1,500 publications in peer reviewed medical journals) to confirm the clinical value of exhaled NO measurement.



Normal epithelial cells. Minimal release of NO.



Activated epithelial cells during inflammation demonstrate increased production of NO.

"...the new studies... ...are highly suggestive of long-term benefit of F_{ENO} inflammometry in asthma management. The bottom line is that F_{ENO} inflammometry is an easy test which is helpful to target steroid treatment, to reduce steroids where possible, and to provide significant benefits in terms of less hyperresponsiveness and less inflammation without leading to overall need for more steroids at the group level. On the basis of these findings, F_{ENO} offers more for day-to-day asthma management than any of the conventional lung function tests."

Editorial, Eur Respir J 2005;26:1-3⁵

CONTENTS

Asthma Management Made Easy	3
F_{ENO} Measures the Inflammation – Not Just the Symptoms	4
How Can F_{ENO} Measurement Help Improve Clinical Decision Making?	5-7
Factors Affecting Exhaled NO Levels	8
References	9
Guide to Interpretation of F_{ENO} Values in Symptomatic Steroid Naïve Patients	10
Guide to Interpretation of F_{ENO} Values in Anti-Inflammatory Treated Patients	11

Asthma Management Made Easy

The measurement of fractional exhaled nitric oxide (F_{ENO}) has been validated as a way of measuring the airway inflammation that underlies asthma.

F_{ENO} measurement is:

- ✓ ***Accurate***
- ✓ ***Reproducible***
- ✓ ***Immediate***
- ✓ ***As informative as biopsy***

F_{ENO} measurement offers:

- ✓ ***Correct asthma diagnosis***
- ✓ ***Rapid identification of non-compliance***
- ✓ ***Insights into steroid effectiveness***
- ✓ ***Prediction of steroid response***
- ✓ ***Steroid dose-titration that reduces cost and improves patient outcome***
- ✓ ***Notification of loss of control***
- ✓ ***Prediction of asthma relapse***

The American Thoracic Society, in conjunction with the European Respiratory Society, have developed guidelines on how exhaled NO measurements should be performed⁶. Measurements performed according to these guidelines are called Fractional Exhaled Nitric Oxide (F_{ENO}). The guidelines state that exhaled NO measurements must be performed at a controlled and standardized exhalation flow rate as the F_{ENO} value is highly flow dependent.

The F_{ENO} values in this brochure are valid for the standardized 50mL/s flow rate only.

FE_{NO} Measures the Inflammation – Not Just the Symptoms

Asthma is, by definition, a chronic inflammatory process – which leads to air-flow limitation and increased responsiveness to asthma triggers. Standard methods for diagnosing and monitoring asthma traditionally focus on symptoms and airway contraction. Until now, routine assessment of the underlying level of inflammation has not been possible.

FE_{NO} measurement is:

- ✓ **Accurate**
- ✓ **Reproducible**
- ✓ **Immediate**
- ✓ **As informative as biopsy**

FE_{NO} measurement is accurate and reproducible when measured with standardized, approved devices. Results are available immediately, allowing the clinician to measure the underlying inflammation while the patient is in the clinic.

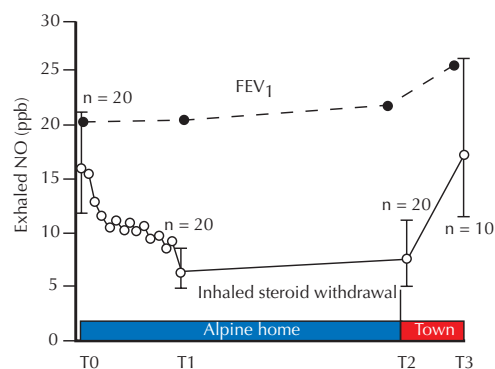
FE_{NO} measurement has been shown to be as informative as biopsy^{1, 2} and bronchoalveolar lavage-techniques^{7, 8} which are the traditional “gold standards” in determining ongoing airway inflammation.

FE_{NO} measurement is comparable to sputum analysis in determining the level of inflammation⁹.

Exhaled NO values increase even before the onset of symptoms or loss of control. This makes FE_{NO} measurement a helpful tool both in predicting loss of control¹⁰ and assessing compliance with inhaled steroids¹¹.

FE_{NO} also responds more rapidly than spirometry to changes in inflammation following allergen exposure, making it a more sensitive marker of the disease^{12, 13}. Spirometry and FE_{NO} are independent measures of different aspects of the disease. So, there is little correlation between FE_{NO} levels and pulmonary function tests in asthma patients.

Change was observed in exhaled NO levels in a group of patients with atopic asthma who were placed in an Alpine home away from their allergens. NO levels fell during the 3 months in the Alpine home and remained stable even when glucocorticoids were withdrawn. Three weeks after returning to their homes, the patients’ exhaled NO levels increased. In comparison, spirometry results continued to improve after the patients returned home¹².



Piacentini, 1999¹²

How Can $F_{E_{NO}}$ Measurement Help Improve Clinical Decision Making?

$F_{E_{NO}}$ measurement has been shown to be **superior to the majority of conventional tests** recommended in international guidelines for diagnosing asthma in symptomatic patients.

$F_{E_{NO}}$ measurement offers:

✓ **Correct asthma diagnosis**

It has been demonstrated that while exhaled air from normal adult subjects typically contains between 5 and 25 parts per billion (ppb) nitric oxide (5 to 20 ppb in children), the exhaled air of asthmatic subjects shows between **double and four times** the normal nitric oxide level.

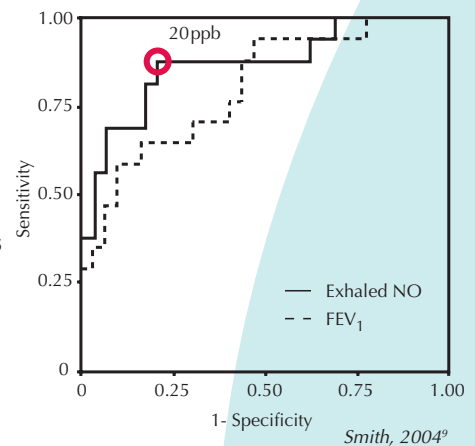
This means that used in conjunction with well-established techniques such as spirometry, $F_{E_{NO}}$ measurement can be used by clinicians to help in the differential diagnosis of eosinophilic bronchial asthma, thereby minimizing inappropriate or ineffective therapy.

$F_{E_{NO}}$ measurement offers the clinician:

Correct asthma diagnosis in over 80% of patients 8-75 years using a cut off of 20ppb⁹.

Correct asthma diagnosis in nearly 80% of children 4-8 years using a cut off of 10ppb¹⁴.

Exhaled NO (solid line) offers a higher degree of diagnostic accuracy for asthma (sensitivity 88% at a cut-off of 20ppb) than tests based on lung function (dotted line). The diagnosis of asthma was ascertained by a positive response to bronchodilator and/or positive bronchial hyperresponsiveness in accordance with ATS guidelines⁹.



$F_{E_{NO}}$ measurement offers:

✓ **Rapid identification of non-compliance**

$F_{E_{NO}}$ measurement provides an **easy to use and non-invasive tool for monitoring adherence to steroid treatment**^{11, 15}.

In clinical practice, elevated $F_{E_{NO}}$ levels in patients taking maintenance doses of inhaled steroids either means the patient is not prescribed enough anti-

inflammatory therapy or not adhering to the therapy prescribed.

Although anti-inflammatory treatment in asthma usually reduces $F_{E_{NO}}$, some patients continue to have elevated $F_{E_{NO}}$ levels, despite steroid treatment. This is most frequently a result of non-compliance, but may

also arise from poor inhalation technique, inadequate steroid dosage, chronic exposure to allergen, or non-eosinophilic airway inflammation as the cause of the asthma. Only rarely will an asthma patient be truly steroid resistant^{16, 17}.

How Can $F_{E_{NO}}$ Measurement Help Improve Clinical Decision Making?

$F_{E_{NO}}$ has been shown to decrease rapidly in asthmatic patients when steroid treatment is started. The decrease is a useful indicator of steroid response.

$F_{E_{NO}}$ measurement offers:

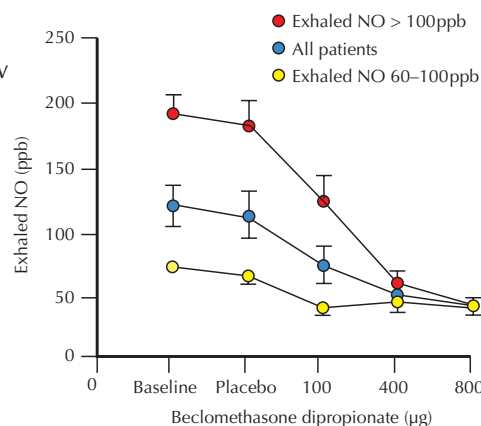
✓ Insights into steroid effectiveness

$F_{E_{NO}}$ responds faster than any other marker to changes in steroid intake^{18, 19}. There is a clear dose-dependent relationship between the inhaled steroid dose and the fall in $F_{E_{NO}}$ level²⁰.

A reduction in $F_{E_{NO}}$ of at least 20% in unstable patients indicates efficacy of the anti-inflammatory treatment²¹. The implication for clinical practice is that monitoring a patient's

$F_{E_{NO}}$ levels before and during anti-inflammatory therapy is now a simple, quick and patient-friendly way of checking that steroid therapy is having the desired effect on airway inflammation^{20, 21}.

The response to varied doses of beclomethasone for patients with initial $F_{E_{NO}}$ values of >100ppb and between 60 to 100ppb.



Silkoff, 2001²⁰

$F_{E_{NO}}$ measurement offers:

✓ Prediction of steroid response

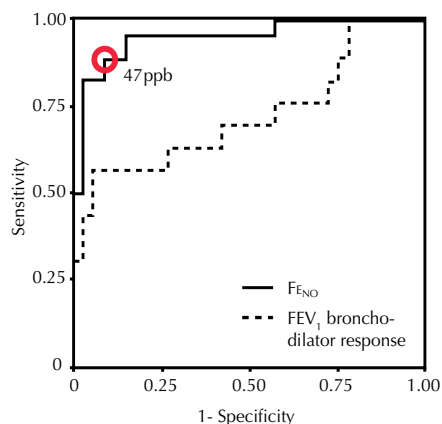
$F_{E_{NO}}$ measurement can be used for immediate and non-invasive identification of steroid responsiveness. **In patients with non-specific symptoms, a $F_{E_{NO}}$ value of >47ppb is highly indicative of a subsequent corticosteroid response**²². $F_{E_{NO}}$ measurement correctly identifies the responders better than spirometry or PEF variability.

Exhaled NO as a predictor of response might help to identify individual children who achieve a greater improvement in asthma control days with an inhaled corticosteroid compared with a

leukotriene receptor antagonist²³.

Patients with normal $F_{E_{NO}}$ levels who do not show any symptomatic response to anti-inflammatory treatment may have little or no underlying inflammation. Other forms of therapy should be considered, and discontinuing of anti-inflammatory treatment may also be appropriate.

In a group of patients with non-specific respiratory symptoms, $F_{E_{NO}}$ measurement was significantly better than FEV_1 bronchodilator response in correctly identifying those who will respond to inhaled fluticasone²².



Smith, 2005²²

F_{ENO} measurement offers:

✓ *Steroid dose-titration that reduces cost and improves patient outcome*

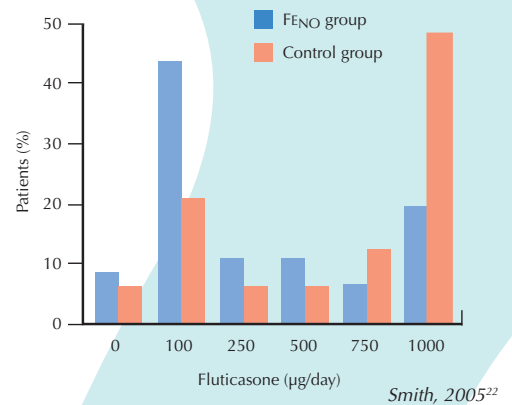
Titrating the steroid dose to match the severity of airway inflammation results in a healthier patient with fewer emergency room visits and significantly fewer exacerbations²⁴.

Several studies have now confirmed that **routine monitoring of the F_{ENO} level as a marker for inflammation makes it possible to titrate the steroid dose according to the patient's specific need**^{25, 26}.

Use of exhaled NO measurements can significantly reduce maintenance doses of inhaled

steroids without compromising asthma control²⁵. In patients already on steroids, the dose can be gradually reduced just to the point at which the F_{ENO} level starts to rise. Then the steroid dose should be raised just enough to keep the F_{ENO} level stable.

Compared to conventional treatment guidelines, steroid titration based on F_{ENO} and symptoms improved asthma prognosis (measured as improved hyper-responsiveness and less inflammation)²⁶.



There was a significant difference in the distribution of doses of inhaled fluticasone at the end of the study. The mean dose was 370 µg/day in the F_{ENO} monitored group and 641 µg/day in the control group. At study end, the control of asthma in the F_{ENO} group was non-significantly better²⁵.

F_{ENO} measurement offers:

✓ *Notification of loss of control*

If a patient's F_{ENO} level increases by over 60% from one visit to the next, even in the absence of asthma symptoms, this increase

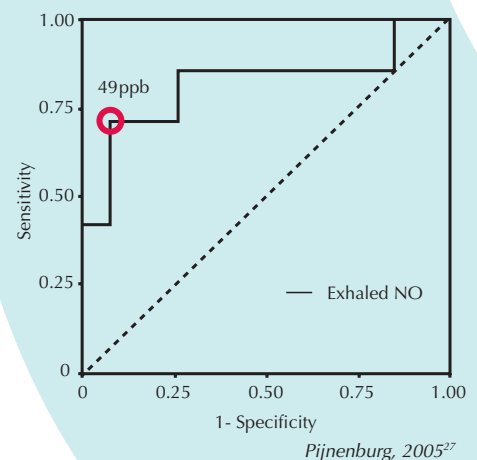
has a **positive predictive value of over 80% of an imminent deterioration in asthma control**¹⁰.

F_{ENO} measurement offers:

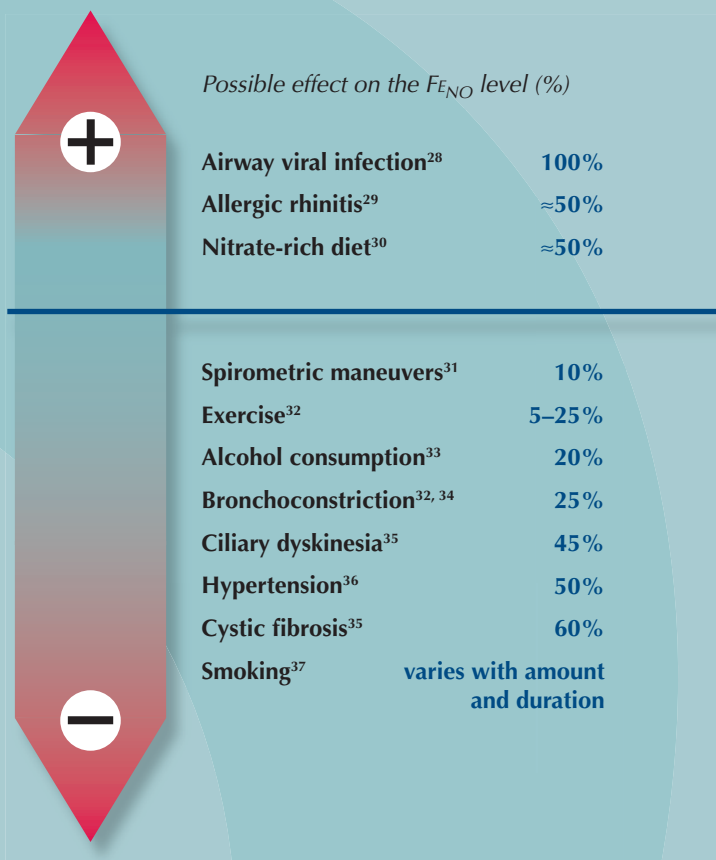
✓ *Prediction of asthma relapse*

When asymptomatic children in clinical remission stopped taking steroids, a F_{ENO} level of more than 49 ppb 2 to 4 weeks later was an effective predictor of asthma relapse²⁷.

A F_{ENO} level higher than 49 ppb 4 weeks after steroid removal was highly indicative of asthma relapse²⁷.



Factors Affecting Exhaled NO Levels



Always perform exhaled NO measurements first, prior to any other respiratory test.

Always check if the patient:

- has an upper or lower airway infection
- is a smoker
- has consumed food or liquid in the past hour

Smoking reduces exhaled NO³⁷. Healthy smokers normally have $F_{E_{NO}}$ levels between 2-10ppb. Increased $F_{E_{NO}}$ levels in smokers are still significant for ongoing eosinophilic inflammation. However, near-normal levels (see page 10 and 11) are difficult to analyze. Results should be interpreted with great caution.

Upper or lower respiratory tract infections may lead to increased $F_{E_{NO}}$ levels.



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Diagnosis

Guide to Interpretation of F_{ENO} Values in Symptomatic Steroid Naïve Patients

Do not use this guide if the patient is a smoker. Data are inconclusive for current smokers.
F_{ENO} values are complementary to spirometry values in the diagnosis and assessment of airway disease.

	LOW	NORMAL	INTERMEDIATE	HIGH
Eosinophilic inflammation	Unlikely	Unlikely	Present, but mild	Significant
ADULTS				
F _{ENO} (ppb)*	< 5	5–25	25–50	> 50
	<p>Consider: Smoker (besides considerations in children)</p>	<p>Consider: Neutrophilic asthma Anxiety/hyper-ventilation Vocal cord dysfunction Rhinosinusitis Gastro-oesophageal reflux Cardiac disease</p>	<p>Interpretation based on clinical presentation</p>	<p>Consider: Atopic asthma if the history is appropriate If FEV₁ < 80% predicted, diagnosis of asthma is very likely Eosinophilic bronchitis Churg-Strauss syndrome A positive response to a trial of inhaled or oral steroid is likely In ex-smokers with COPD this may also be true</p>
CHILDREN (<12 years)				
F _{ENO} (ppb)*	< 5	5–20	20–35	> 35
	<p>Consider: Primary ciliary dyskinesia (check nasal NO) Cystic fibrosis Chronic lung disease of prematurity</p>	<p>Consider: Wheezy bronchitis Gastro-oesophageal reflux ENT disorders Neutrophilic asthma Vocal cord dysfunction Anxiety/hyper-ventilation Immunodeficiencies</p>	<p>Interpretation based on clinical presentation</p>	<p>If combined with any objective evidence of reversible airway obstruction, asthma is very likely and a positive response to a trial of inhaled or oral steroids is likely</p>

Management

Guide to Interpretation of F_{ENO} Values in Anti-Inflammatory Treated Patients

Do not use this guide if the patient is a smoker. Data are inconclusive for current smokers.

F_{ENO} values are complementary to spirometry values in the diagnosis and assessment of airway disease.

	LOW	NORMAL	INTERMEDIATE	HIGH
Eosinophilic inflammation	Unlikely	Unlikely	Present, but mild	Significant
ADULTS				
F _{ENO} (ppb)*	< 5	5–25	25–50	> 50 Or a rise of 60% or more since previous measurement
	<p>Consider: Smoker (besides considerations in children)</p>	<p>If symptomatic, review diagnosis: Neutrophilic asthma Anxiety/hyperventilation Vocal cord dysfunction Rhinosinusitis Gastro-oesophageal reflux</p> <p>If asymptomatic: Implies good compliance with treatment. Reduce dose or, in case of low ICS dose, even withdraw ICS altogether</p>	<p>If symptomatic, consider: Infection as reason for worsening High levels of allergen exposure Adding in other therapy apart from ICS (e.g. long acting β-agonist) Consider ICS dose increase</p> <p>If asymptomatic: No change in ICS dose, if patient is stable</p>	<p>If symptomatic, consider: Inadequate ICS treatment: (1) check compliance (2) check for poor inhaler technique (3) inadequate ICS dose Continuous high level allergen exposure Imminent exacerbation or relapse depending on history of individual patient (more likely if ICS dose is zero) Steroid resistance (rare)</p> <p>If asymptomatic: No change in ICS dose, if patient is stable</p>
CHILDREN (<12 years)				
F _{ENO} (ppb)*	< 5	5–20	20–35	> 35 Or a rise of 60% or more since previous measurement
	<p>Consider: Primary ciliary dyskinesia Cystic fibrosis Chronic lung disease</p>	<p>If symptomatic, review diagnosis: Wheezy bronchitis Gastro-oesophageal reflux ENT disorders Neutrophilic asthma Vocal cord dysfunction Anxiety/hyperventilation Immunodeficiencies</p> <p>If asymptomatic: Implies good compliance with treatment. Reduce dose or, in case of low ICS dose, even withdraw ICS altogether</p>	<p>If symptomatic (besides considerations in adults), consider: Possible inadequate ICS treatment: (1) check compliance (2) check for poor inhaler technique and consider metered dose inhaler and spacer if patient is currently using a dry powder device</p> <p>If asymptomatic: No change in ICS dose, if patient is stable</p>	<p>If symptomatic (besides considerations in adults), consider: Metered dose inhaler and spacer if patient is currently using a dry powder device</p> <p>If asymptomatic: No change in ICS dose, if patient is stable</p>

For references and information of exhaled NO in asthma see the Scientific Background – Exhaled Nitric Oxide, A Noninvasive Marker for Inflammation, issued by Aerocrine.

*At 50 mL/s flow rate.

Partly based on Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;61:817-27.

F_{ENO} – Fractional Exhaled Nitric Oxide

Want to know more?

Nearly 1,500 clinical papers related to the use of F_{ENO} measurement in exhaled breath have been published in peer reviewed journals;

Visit www.aerocrine.com, F_{ENO} in Clinical Practice, to view the abstracts.

For a more detailed review of available literature about exhaled NO in asthma, please refer to the annually updated **Scientific Background** published by Aerocrine.

Aerocrine sells CE marked and FDA cleared exhaled NO systems that provide repeatable, trustworthy results as proven in GCP clinical trials. Using a standardized, approved and accurate device is essential for the interpretation and application of exhaled NO values.

Based on the company's intellectual property, Aerocrine develops and commercializes products for the monitoring of nitric oxide (NO) as a marker of inflammation, to improve the management and care of patients with inflammatory disease in the airways.

Patents:

US Patent 5,447,165, US Patent 5,922,610, US Patent 6,038,913, US Patent 6,063,027, US Patent 6,099,480, US Patent 6,149,606, US Patent 6,183,416, US Patent 6,511,425, US Patent 6,626,844, US Patent 6,723,056, US Patent 6,761,185, US Patent 7,014,692 and patents pending.



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