EXHALED NITRIC OXIDE MEASUREMENT IN DIAGNOSE AND MANAGE ASTHMA

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ANNOTATE

- FENO: Fractional concentration of exhaled nitric oxide
- $J'aw_{NO}$: airway NO production
- CANO: alveolar concentration of NO

CONTENTS:

- Introduction
- FeNO in diagnose asthma
- FeNO in manage asthma

+ Predicting response to corticosteroids

+ Contribution of FeNO on inhaled corticosteroid adjustment

INTRODUCTION

- Nitric oxide (NO) is produced by the human lung and present in the exhaled breath. It has been implicated in the pathophysiology of lung diseases, including asthma.
- The measurement of exhaled NO is more common for the non-invasive detection and quantification of airway inflammation.

INTRODUCTION

- Compared to existing pulmonary function tests, FeNO has clear advantages: non-invasive for the patient, easy to perform, allowing detecting airway inflammation.
- It supports the diagnosis of asthma , enables better phenotyping asthmatic patients, regarding their cortico-sensitivity.

INTRODUCTION

- In practice, analysis relationship between expiratory flow rate and NO concentration allows determining, the bronchial NO production capacity and alveolar NO concentration, thus distinguishing the respective contributions of both NO-producing compartments.

INTRODUCTION

- Fractional concentration of exhaled nitric oxide (FENO) is made by the addition of alveolar concentration of NO (CANO) with the ratio of maximum airway flux of NO (J'awNO) to expiratory flow when expiratory flow is low (50 mL/s)
- Most exhaled NO found in low exhaled flow rates is produced by the airways. During atopy (with or without asthma), there is an increase in airway NO production (J'aw_{NO}), explaining the increase in FE_{NO} . In asthma, J'awNO (and FE_{NO}) corre-lates with the eosinophilic airway inflammation.

Predictive value of FENO in diagnosing asthma

- FeNO can help in the diagnosis of asthma when clinical symptoms are non-specific and pulmonary function tests are normal.
- FeNO has a better predictive value than conventional pulmonary function tests such as the forced expiratory volume in one second (FEV_1), the FEV_1 /forced vital capacity ratio and changes in peak expiratory flow rate (PEFR)
- Compared to other bronchial challenge tests (methacholine, exer-cise, adenosine-5'-monophosphate), FeNO is faster and there is no risk of bronchial obstruction .

1 STUDY

Am J Respir Crit Care Med. 2004 Feb 15;169(4):473-8. Epub 2003 Nov 25.

Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests.

Smith AD[1], Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR.

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Abstract

International guidelines recommend a range of clinical tests to confirm the diagnosis of asthma. These focus largely on identifying variable airflow obstruction and responses to bronchodilator or corticosteroid. More recently, exhaled nitric oxide (FE(NO)) measurements and induced sputum analysis to assess airway inflammation have been highlighted. However, to date, no systematic comparisons to confirm the diagnostic utility of each of these methods have been performed. To do so, we investigated 47 consecutive patients with symptoms suggestive of asthma, using a comprehensive fixed-sequence series of diagnostic tests. Sensitivities and specificities were obtained for peak flow measurements, spirometry, and changes in these parameters after a trial of steroid. Comparisons were made against FE(NO) and sputum cell counts. Sensitivities for each of the conventional tests (0-47%) were lower than for FE(NO) (88%) and sputum eosinophils (86%). Overall, the diagnostic accuracy when using FE(NO) and sputum eosinophils was significantly greater. Results for conventional tests were not improved, using a trial of steroid. We conclude that FE(NO) measurements and induced sputum analysis are superior to conventional approaches, with exhaled nitric oxide being most advantageous because the test is quick and easy to perform.

Table 2 Specificity, sensitivity and predictive value of exhaled NO measurement in asthma. It should be noted that the exhaled NO has always a high negative predictive value from one study to another.

Indications	Threshold (ppb)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Authors (Ref.)
Diagnosis of asthma in subjects with						
Non-specific respiratory symptoms	20	88	79	70	92	Smith et al. [36]
Chronic cough	30	75	87	60	93	Chatkin et al. [37]
The same	40	88	83	73	93	Kowal et al. [38]
The same	32	86	76	47	95	Oh et al. [39]
Responses to glucocorticoids in subjects with						
Non-specific respiratory symptoms	47	82	91	82	91	Smith et al. [40]
Chronic cough	38	90	85	90	85	Hahn et al. [41]
Severe asthma	30	88	91	88	91	Pérez-de-Llano et al. [42]

RECOMMENNDATION FROM ATS GUIDELINE

An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FE_{NO}) for Clinical Applications

Raed A. Dweik, Peter B. Boggs, Serpil C. Erzurum, Charles G. Irvin, Margaret W. Leigh, Jon O. Lundberg, Anna-Carin Olin, Alan L. Plummer, D. Robin Taylor, on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FE_{NO}) for Clinical Applications

This Official Clinical Practice Guideline of the American Thoracic Society (ATS) was approved by the ATS Board Of Directors, May 2011

CONTENTS

Background: Measurement of fractional nitric oxide (NO) concentration in exhaled breath (FE_{NO}) is a quantitative, noninvasive, simple, and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. While FE_{NO} measurement has been standardized, there is currently no reference guideline for practicing health care providers to guide them in the appropriate use and interpretation of FE_{NO} in clinical practice.

Purpose: To develop evidence-based guidelines for the interpretation of FE_{NO} measurements that incorporate evidence that has accumulated over the past decade.

Methods: We created a multidisciplinary committee with expertise in the clinical care, clinical science, or basic science of airway disease and/or NO. The committee identified important clinical questions, synthesized the evidence, and formulated recommendations. Recommendations were developed using pragmatic systematic reviews of the literature and the GRADE approach.

Results: The evidence related to the use of FE_{NO} measurements is reviewed and clinical practice recommendations are provided.

Conclusions: In the setting of chronic inflammatory airway disease including asthma, conventional tests such as FEV_1 reversibility or provocation tests are only indirectly associated with airway inflammation. FE_{NO} offers added advantages for patient care including, but not limited to (*1*) detecting of eosinophilic airway inflammation, (*2*) determining the likelihood of corticosteroid responsiveness, (*3*) monitoring of airway inflammation to determine the potential need for corticosteroid, and (*4*) unmasking of otherwise unsuspected nonadherence to corticosteroid therapy.

RECOMMENNDATION FROM ATS GUIDELINE

Strong recommendation.

- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not
- Clinicians: Most patients should receive the recommended course of action
- Policy makers: The recommendation can be adopted as a policy in most situations

Weak recommendation.

- Patients: The majority of people in this situation would want the recommended course of action, but many would not
- Clinicians: Be more prepared to help patients to make a decision that is consistent with the patient's own values
- Policy makers: There is a need for substantial debate and involvement of stakeholders

RECOMMENNDATION FROM ATS GUIDELINE

in the recommendation. If not stated, then the recommendation applies to patients with asthma.

- We recommend the use of F_{ENO} in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- We recommend the use of F_{ENO} in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation (strong recommendation, low quality of evidence).
- We suggest that F_{ENO} may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence).
- We suggest the use of cut points rather than reference values when interpreting F_{ENO} levels (weak recommendation, low quality of evidence).
- We recommend accounting for age as a factor affecting F_{ENO} in children younger than 12 years of age (strong recommendation, high quality of evidence).
- We recommend that low F_{ENO} less than 25 ppb (< 20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).
- We recommend that F_{ENO} greater than 50 ppb (> 35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).
- We recommend that F_{ENO} values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context. (strong recommendation, low quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of F_{ENO} (strong recommendation, moderate quality of evidence).
- We recommend the use of F_{ENO} in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).
- We suggest using the following values to determine a significant increase in F_{ENO}: greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next (weak recommendation, low quality of evidence).
- We suggest using a reduction of at least 20% in F_{ENO} for values over 50 ppb or more than 10 ppb for values lower than 50 ppb as the cut point to indicate a significant response to antiinflammatory therapy (weak recommendation, low quality of evidence).

Conclusion: Advances in technology and standardization have made F_{ENO} measurement simple, permitting its use as a biomarker that adds a new dimension to the traditional clinical tools in the assessment and management of airways diseases. These guidelines for interpretation of F_{ENO} measurements are meant to enhance their clinical utility, but more work is still needed to better define the use of F_{ENO} in different clinical settings.

BTS Guideline asthma 2014

3.2.2 TESTS OF EOSINOPHILIC AIRWAY INFLAMMATION

Eosinophilic inflammation in children can be assessed non-invasively using induced sputum differential eosinophil count or exhaled nitric oxide concentrations (FE_{NO}).

Sputum induction is feasible in school-aged children.[61, 62] Higher sputum eosinophil counts are associated with more marked airways obstruction and reversibility, greater asthma severity and atopy.[63] In children with newly diagnosed mild asthma, sputum eosinophilia is present and declines with ICS treatment.[62] Sputum induction is possible in approximately 75% of children tested, but it is technically demanding and time consuming and at present remains a research tool. 2^{++}

It is feasible to measure FE_{NO} in unsedated children from the age of 3–4 years.[64] A raised FE_{NO} is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma.[65] FE_{NO} is closely linked with atopic status, age and height.[66, 67] In some studies, FE_{NO} correlated better with atopic dermatitis and allergic rhinitis than with asthma. It is not closely linked with underlying lung function. Measuring FE_{NO} could not differentiate between groups once atopy was taken into account.[68] Home measurements of FE_{NO} have a highly variable relationship with other measures of disease activity and vary widely from day to day.[69] 2^{+}

BTS Guideline asthma 2014

Table 7: Estimates of sensitivity and specificity of test results in adults with suspected asthma and normal or near-normal spirometric values[75,81,83]

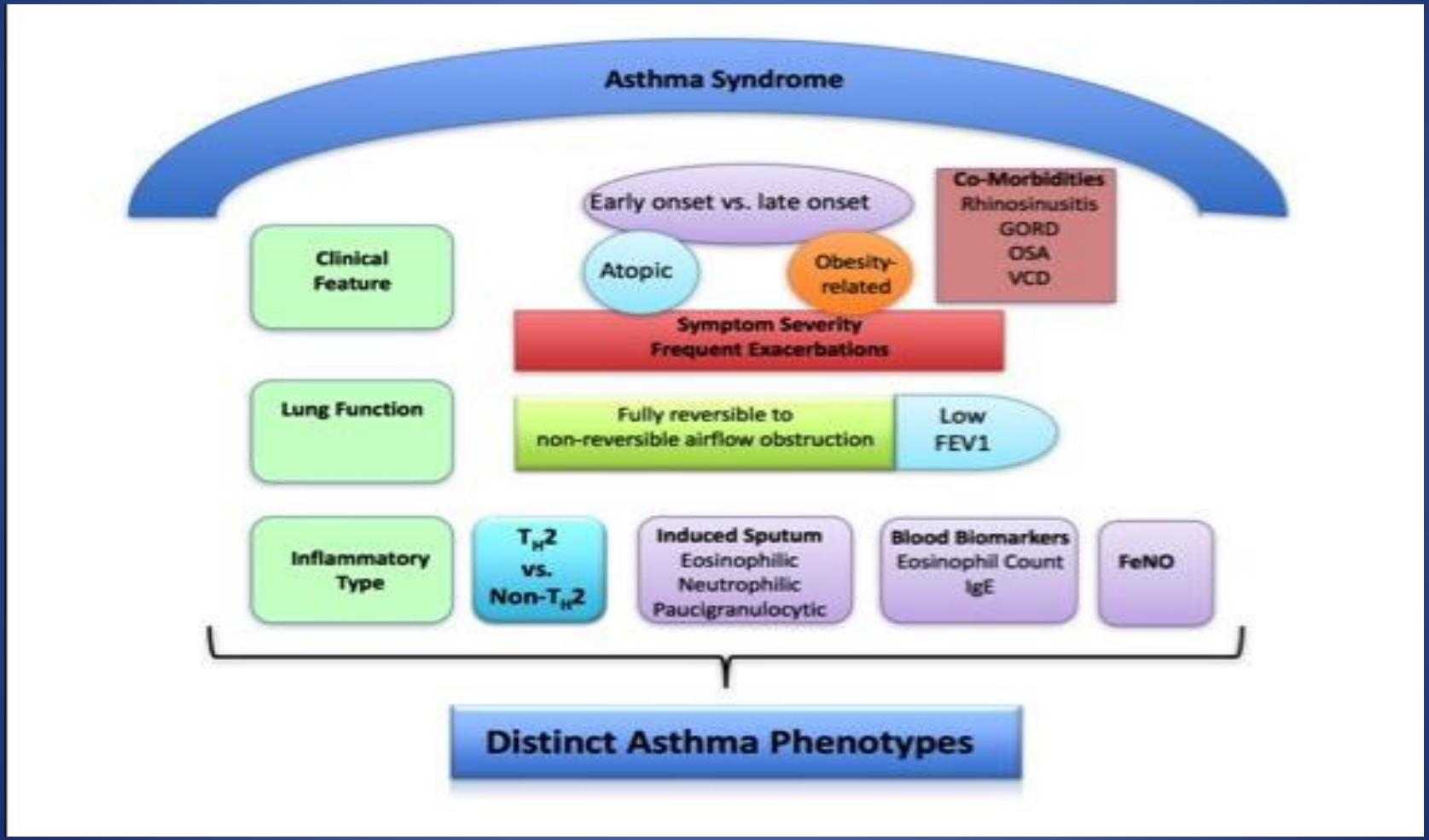
Test	Normal range	Validity	
		sensitivity	specificity
Methacholine PC_{20}	>8 mg/ml	High	Medium
Indirect challenges*	varies	Medium****	High
FE_{NO}	<25 ppb	High****	Medium
Sputum eosinophil count	<2%	High****	Medium
PEF A%H	<8** <20%***	Low	Medium

PC_{20} = the provocative concentration of methacholine required to cause a 20% fall in FEV_1. FE_{NO} = exhaled nitric oxide concentration. PEF A%H = peak expiratory flow amplitude per cent highest. ppb = parts per billion.

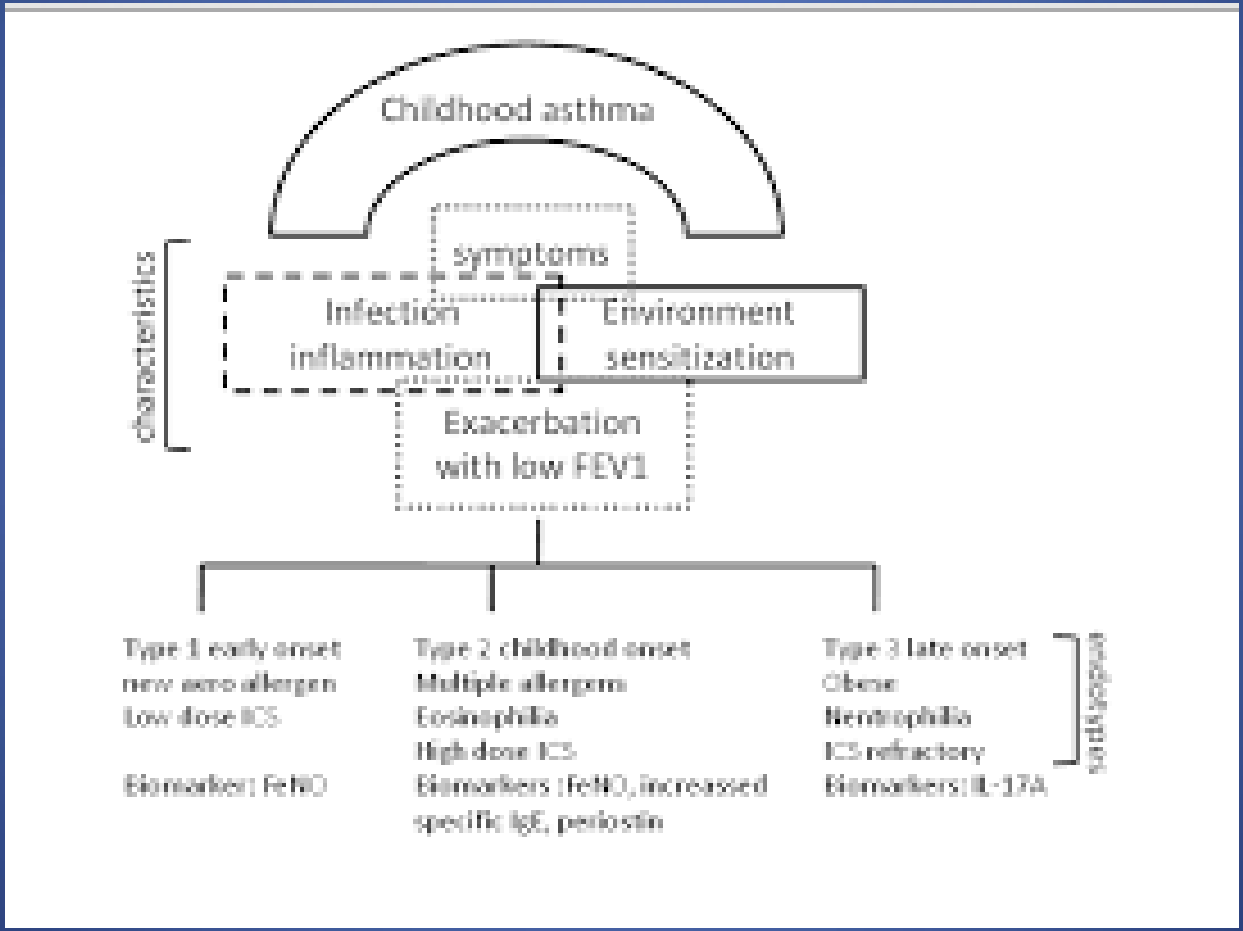
Predictive value of FeNO on the response to corticosteroids

- Treatment: Not all patients respond to corticosteroids, an important reason to use FENO is to help decide who might benefit from steroid treatment, and who should try other medications. The optimum cut point in the study by Smith and coworkers, was 47 ppb, with a negative predictive value of 89% for the change in FEV1 with inhaled steroids.(ATS 2011)

ASTHMA PHENOTYPES



ASTHMA PHENOTYPES



Exhaled Nitric Oxide

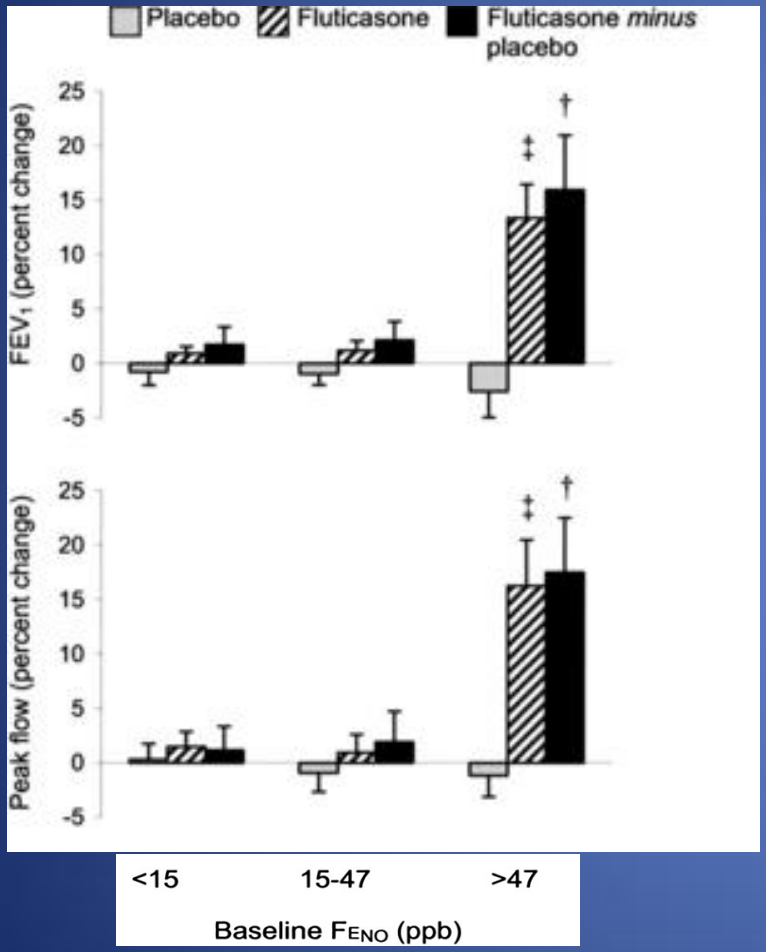
A Predictor of Steroid Response

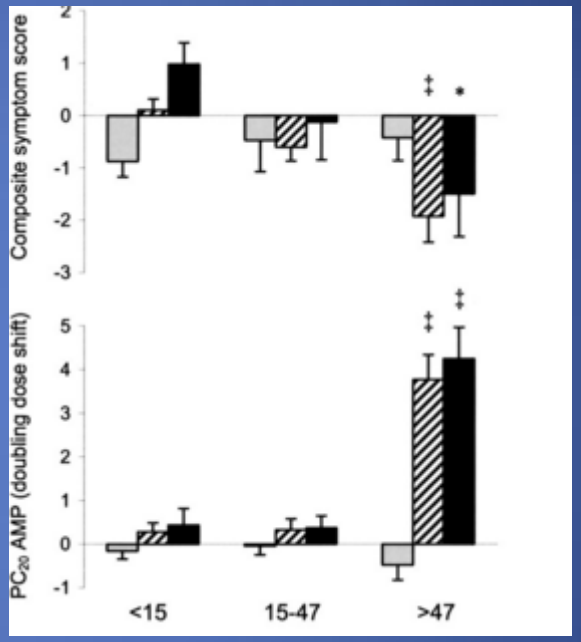
Andrew D. Smith, **Jan O. Cowan**, **Karen P. Brassett**, **Sue Filsell**, **Chris McLachlan**, **Gabrielle Monti-Sheehan**, **G. Peter Herbison**, and **D. Robin Taylor**

ABSTRACT Choose

Rationale: The initial management of patients who present with persistent respiratory symptoms includes recognizing those with the potential to benefit from inhaled steroid therapy. To date, this has required undertaking a "trial of steroid" to identify responders. There is increasing evidence that steroid response is more likely in patients with eosinophilic airway inflammation, and this can be assessed indirectly using exhaled nitric oxide (FE_{NO}) measurements. *Objectives:* We aimed to assess the predictive accuracy of FE_{NO} to identify steroid response in 52 patients presenting with undiagnosed respiratory symptoms in a single-blind, fixed-sequence, placebo-controlled trial of inhaled fluticasone for 4 weeks. *Methods:* Comparisons of predictive accuracy were made between FE_{NO} and other conventional predictors: peak flows, spirometry, bronchodilator response, and airway hyperresponsiveness measured at baseline. "Steroid response" was defined as change in symptoms, peak flows, spirometry, or airway hyperresponsiveness to adenosine based on established guidelines and recommendations. *Results:* Steroid response was significantly greater in the highest FE_{NO} tertile (> 47 ppb) for each endpoint. This outcome was independent of the diagnostic label. The predictive values for FE_{NO} were significantly greater than for almost all other baseline predictors, with an optimum cut point of 47 ppb. *Conclusions:* FE_{NO} measurements greater than 47 ppb provide a means of predicting steroid response in patients with undiagnosed respiratory symptoms. Assessing airway inflammation is of more practical value than diagnostic labeling when considering the potential usefulness of inhaled antiinflammatory therapy.

RESULT


Placebo
Fluticasone
Fluticasone *minus* placebo
FEV1 (percent change)
Peak flow (percent change)
25
20
15
10
5
0
-5
‡
†
<15
15-47
>47
Baseline FENO (ppb)


Composite symptom score
PC20 AMP (doubling dose shift)
2
1
0
-1
-2
-3
5
4
3
2
1
0
-1
‡
*
<15
15-47
>47
Baseline FENO (ppb)

Contribution of FeNO on inhaled corticosteroid adjustment

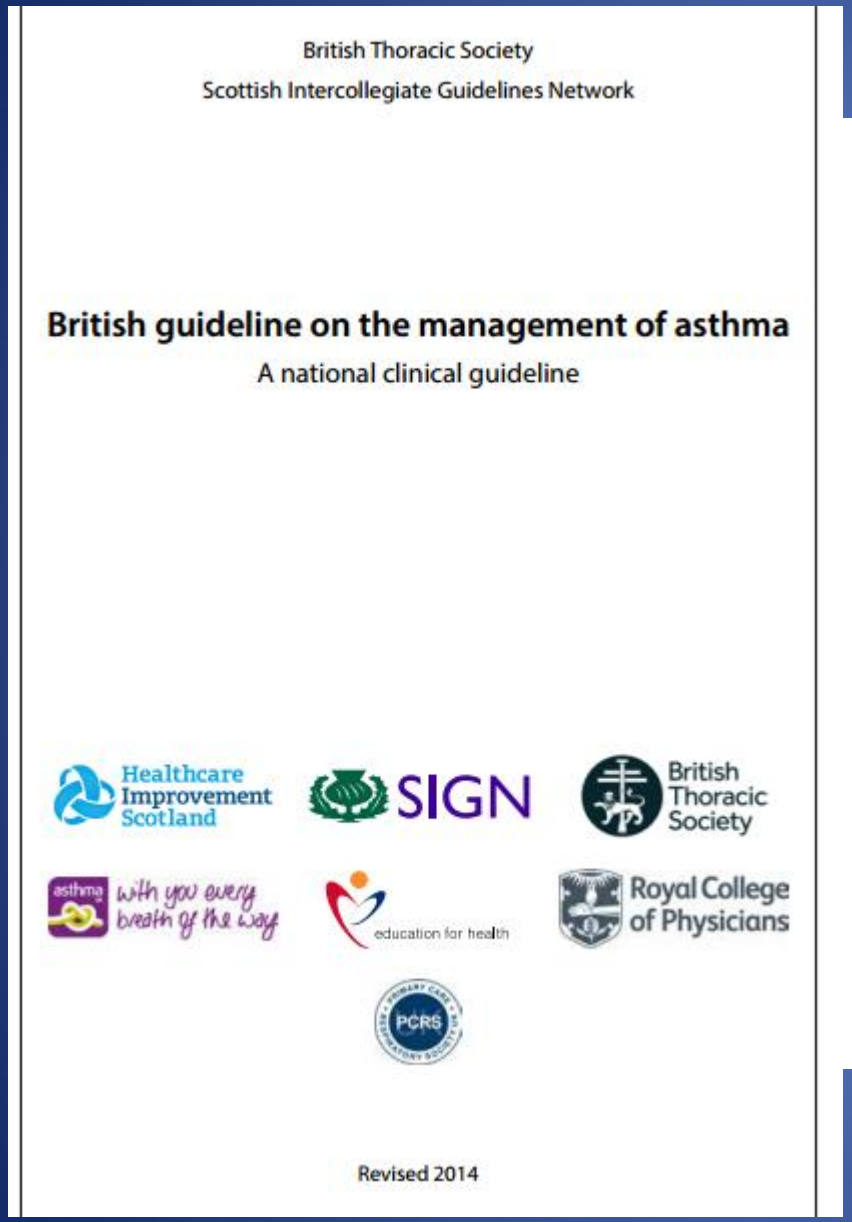
British guideline on the management of asthma 2014 (BTS) :

3.6.1 MONITORING ASTHMA IN CHILDREN

Biomarkers

Studies in children have shown that routine serial measurements of peak expiratory flow,[111-113] airway hyper-responsiveness[114] or FE_{NO}[115-118] do not provide additional benefit when added to a symptom-based management strategy as normal lung function does not always indicate well controlled asthma. One clinical trial, however, reported that a 90-day average seasonal 5% reduction in peak flow was associated with a 22% increase in risk of asthma attack (p=0.01).[119] In a further study of children with asthma who were not taking ICS, compared with children with an FEV_1 ≥100%, children with FEV_1 80% to 99%, 60% to 79%, and <60% were 1.3, 1.8, and 4.8, respectively, more likely to have a serious asthma attack in the following four months.[120]

A small prospective observational study in 40 children suggested that serial measurements of FE_{NO} and/or sputum eosinophilia may guide step down of ICS.[121] Another small study of 40 children showed that a rising FE_{NO} predicted relapse after cessation of ICS.[117] The number of children involved in these step-down and cessation studies is small and the results should be interpreted with some caution until replicated in larger datasets.



	predicted).		
Exhaled nitric oxide (FE_{NO})[82, 89, 107, 117, 121, 136, 137]	Increasingly available in secondary care. Monitors still relatively expensive although expect the technology to become cheaper and more widespread. Measurements can be obtained in almost all adults and most children over 5 years. Results are available immediately. Reasonably close relationship between FE_{NO} and eosinophilic airway inflammation, which is independent of gender, age, atopy and ICS use. Relationship is lost in smokers. Not closely related to other measures of asthma morbidity.	Normal range <25 ppb at exhaled flow of 50 ml/sec. 95% range for repeat measure 4 ppb. >50 ppb highly predictive of eosinophilic airway inflammation and a positive response to corticosteroid therapy. <25 ppb highly predictive of its absence of and a poor response to corticosteroids or successful step down in corticosteroid therapy.	Raised FE_{NO} (>50 ppb in adults and >35 ppb in children) is predictive of a positive response to corticosteroids. The evidence that FE_{NO} can be used to guide corticosteroid treatment is mixed. Protocols for diagnosis and monitoring have not been well defined and more work is needed. Low FE_{NO} (<25 ppb in adults; <20 ppb in the under 12 year old range) may have a role in identifying patients who can step down corticosteroid treatment safely.

CONCLUSION

Table 4 Usefulness of exhaled NO measurement in the detection of bronchial inflammation in asthma.

Asthma is suspected (without having been formally diagnosed) in a patient with

- Atypical symptoms or whose description is vague (with or without atopy, with or without known bronchial hyperresponsiveness)
  - High[a] FE_{NO} values help in the diagnosis of asthma
  - Low FE_{NO} values do not allow ruling out the diagnosis of asthma
- Typical symptoms
  - High FE_{NO} values increase the likelihood of allergic asthma
  - Normal or low FE_{NO} values reduce the likelihood of presence of a sensitization to an allergen present in patient environment

Asthma is known but uncontrolled in a patient who has not yet received inhaled corticosteroids (or receiving low doses)

- High FE_{NO} values increase the likelihood of efficacy of corticosteroids (dose initiation or increase) or of management of a poor compliance
- Normal or low FE_{NO} values do not exclude the therapeutic test with inhaled corticosteroids

Asthma is known and controlled in a patient treated with inhaled corticosteroids

- High FE_{NO} values support maintaining doses of inhaled corticosteroid if they are intermediate or high[b] but should not encourage to increase the dose in patients treated with low-dose inhaled corticosteroids
- Intermediate or low FE_{NO} values support a decrease in inhaled corticosteroids in patients treated with high-dose inhaled corticosteroids and are against an increase in corticosteroids in patients treated with low-dose inhaled corticosteroids

Asthma is known but uncontrolled in a patient already treated with inhaled corticosteroids at maximum doses

- High FE_{NO} values increase the likelihood of efficacy of anti-IgE treatment

[a] Criteria for high (> 50 ppb in adults, > 35 ppb in children), intermediate (25–50 ppb in adults, 20–35 ppb in children) or low (< 25 ppb in adults, < 20 ppb in children) FE_{NO} values are those of the latest ATS recommendations [10].

[b] The dose of inhaled corticosteroids is considered low if $\leq 200\,\mu g$, intermediate if ranging between 200 and 400 μg and high if $> 400\,\mu g$ daily beclomethasone equivalent.

References

- British guideline on the management of asthma 2014
- An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO)for Clinical- May 2011.
- Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, Herbison GP, Taylor DR. Exhaled nitric oxide: a predictor of steroid response.

XIN CÁM ƠN!