

What is FeNO and How Can it Help Asthma Patients?



1

1

Disclaimer

I recognize that I must follow all guidelines and criteria regarding vested interest. I have the following real or perceived conflicts of interest that relate to this presentation:



I am an employee of Methapharm Respiratory, Inc.

- Provocholine® (methacholine chloride)
- Aridol (mannitol)
- Vivatmo pro (FeNO)

Heather Murgatroyd, BA, RRT, CPFT, AE-C




2

2

Objectives

Following this presentation the learner will:

- Define and discuss what fractional exhaled nitric oxide (FeNO) is and what it reveals
- Identify the indications for FeNO measurements both in diagnostics and management
- Recognize guideline support FeNO usage



3

3

Question 1

I have worked with FeNO

A. Yes
B. No

4

4

Nitric Oxide

NO

- Nitric oxide, also nitrous oxide ("laughing gas"), is a gaseous molecular compound with the chemical formula of NO.
- NO is produced in numerous tissues of the body, including the lining, wall of vessels of the arterial branch of coronary.
- NO also has other functions, including a role in inflammation.
- In the lung, NO has functions that include regulation of vascular smooth muscle contraction and bronchodilation.
- Increased NO levels are released from endothelial cells of the arterial wall in the artery lumen in response to inflammation.

nitro
pharm
A Division of Abbott Laboratories

5

5

What is Nitric Oxide

Not to be confused with nitrous oxide, N₂O, or "laughing gas," NO is a gaseous molecular compound with the chemical formula of NO.


nitro
pharm
A Division of Abbott Laboratories

6

6

What is Nitric Oxide

Is produced in numerous tissues of the body, including the lungs, and is present in the exhaled breath of humans.




7

7

What is Nitric Oxide

In the lung, NO has functions that include regulation of vasodilation, neurotransmission, and bronchodilation.




8

8

What is Nitric Oxide

NO also has other functions, including a role in inflammation.



9

9

What is Nitric Oxide

In the presence of allergic inflammation, increased levels of NO are released from epithelial cells of the bronchial wall into the airway lumen.

Novartis
A Division of **Novartis**

10

10

Question 2

FeNO is released by the epithelial cells in the lungs.

A. True
B. False

11

11

Nitric Oxide Release

NORMAL
Epithelial cells release minimal NO

INFLAMMATION
Activated epithelial cells increase production of NO

NITRIC OXIDE


Novartis
A Division of **Novartis**

13

13

FeNO is

- Quantitative
- Noninvasive
- Simple
- Safe
- Standardized




Novopharm
A Division of Novartis

14

14

Indications for FeNo

2021 – American Thoracic Society (ATS) recommendation – “In patients with asthma in whom treatment is being considered, we suggest the use of FENO testing in addition to usual care over usual care alone”




15

15

Indications for FeNo

Intended use of available FeNO devices:

- o **Vivatmo pro** Nitric Oxide Test is a portable, non-invasive device to measure fractional exhaled nitric oxide (FeNO) in human breath.
- o **NIOX VERO®** measures Nitric Oxide (NO) in human breath.
- o **Bedfont NObreath®** is a breath nitric oxide (NO) test system intended to measure fractional exhaled nitric oxide
- o **Fenom Pro** is a portable, non-invasive device to measure fractional exhaled nitric oxide in human breath.



16

16

FeNO & Diagnosis



17

17

Diagnosing Asthma

- No single diagnostic test for asthma
- Asthma is misdiagnosed in 1/2 of patients, which can result in inappropriate or ineffective treatments for patients.
- Spirometry with pre/post bronchodilator to support (or not support) the diagnosis
- FeNO measurement can identify airway inflammation often seen in asthma

18

18

Question 3

Which of the following tests can be used to measure airway inflammation:

- A. sputum/blood eosinophils
- B. Spirometry with pre and post bronchodilator
- C. Indirect Bronchial challenge tests
- D. A & C
- E. All of the above

19

19

4 Pillars of Asthma Diagnosis

21

21

FeNO in Diagnostics

TESTS SUCH AS SPIROMETRY WITH PRE AND POST BRONCHODILATOR OR DIRECT CHALLENGE TESTS ARE ONLY INDIRECTLY ASSOCIATED WITH AIRWAY INFLAMMATION (AHR).

22

22

FeNO in Diagnostics

FENO OFFERS INSIGHT FOR DIAGNOSING PROPERLY BY DETECTING INFLAMMATION

FENO CORRELATES WELL WITH INFLAMMATION AS MEASURED IN SPUTUM, THUS PROVIDING A NON-INVASIVE MEANS TO ASSESS IN ASTHMA.

S. Khatri, J. Iaccarino, et al. (2021) American Thoracic Society Documents. An Official ATS Clinical Practice Guideline: Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma

23

23

FeNO in Diagnostics

FENO MEASUREMENT IDENTIFIES THE LIKELIHOOD OF CORTICOSTEROID RESPONSIVENESS


FENO >47 PPB PREDICTED A POSITIVE RESPONSE TO ICS.


Wang Z, Platts-Rouge P, Knight K, Zeman F, et al. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. 2017
Date

24

24

FeNO & Patient Management





Focused on Every Breath

25

25

Question 4

An elevated FeNO confirms _____, a non-elevated FeNO confirms _____

- A. Asthma/Sarcoidosis
- B. T2 asthma/Exercise Induced Asthma
- C. Airway inflammation/atopy
- D. Likely positive ICS response/possible non T2 driven-asthma

26

26

FeNO


FeNO measurement may be used to complement other objective tests to aid in diagnosis.

An elevated FeNO level does not make a diagnosis of asthma.

- FeNO is a biomarker of allergic (T2) airway inflammation and can support the diagnosis

A non-elevated FeNO level does not mean that the patient does not have asthma.

- The background pathology is not always T2-driven and other types of inflammation that are not responsive to ICS may be present
- The patient may not be exposed to allergens at the time of testing




28

28

Interpreting FeNO


- When FeNO levels are used in monitoring patients, the current level is considered, but also the change in level from previous measurements should be considered
- ATS guidelines state that the change in FeNO after intervention with ICS may be more valid than the absolute FeNO level.
- ATS also recommends that a current FeNO reflecting a 40% increase from previously stable levels should be interpreted as a high FeNO



29

29

FeNO	Adults Children	< 25 ppb < 20 ppb	25-50 ppb 20-35 ppb	> 50 ppb > 35 ppb
Diagnosis				
Symptoms present During past 6 weeks	<ul style="list-style-type: none"> Eosinophilic airway inflammation unlikely Alternative diagnosis Unlikely to benefit from ICS* 	<ul style="list-style-type: none"> Be cautious Evaluate clinical context Monitor change in FeNO over time 	<ul style="list-style-type: none"> Eosinophilic airway inflammation present Likely to benefit from ICS 	
Monitoring (in patients with diagnosed asthma)				
Symptoms present	<ul style="list-style-type: none"> Possible alternative diagnoses Unlikely to benefit from increase in ICS 	<ul style="list-style-type: none"> Persistent allergen exposure Inadequate ICS dose Poor adherence Steroid resistance 	<ul style="list-style-type: none"> Persistent allergen exposure Inadequate ICS dose Poor adherence or inhaler technique Steroid resistance Risk of exacerbation 	
Symptoms absent	<ul style="list-style-type: none"> Adequate ICS dose Good adherence ICS taper 	<ul style="list-style-type: none"> Adequate ICS dosing Good adherence Monitor change in FeNO 	<ul style="list-style-type: none"> ICS withdrawal or dose reduction may result in relapse Poor adherence or inhaler technique 	



Interpreting FeNO

30

30

What Factors Can Affect FeNO Levels

↑ Factors increasing FeNO values	↓ Factors decreasing FeNO values
<ul style="list-style-type: none"> ▶ Bronchodilatation² → FeNO measurement before bronchodilatation ▶ Increased airway caliber^{3,4} → height as a surrogate parameter ▶ Food and Beverages potentially^{1,4} → do not drink or eat before measurement ▶ Atopy^{3,4} ▶ Respiratory tract infections³ ▶ Age^{3,7} 	<ul style="list-style-type: none"> ▶ Bronchoconstriction^{2,6} → FeNO measurement before Provocation ▶ Spirometry reduces FeNO values for duration of approx. 30 min afterwards² → FeNO measurement before Spirometry ▶ Increased mucus production⁶ → FeNO measurement before Sputum induction ▶ Smoking⁶ ▶ Gender, female^{3,4}

31

Question 5

Spirometry provides complete information on airway inflammation.

A. True
B. False

32

Why is FeNO important in asthma management


- Despite the importance of inflammation in the pathophysiology of asthma, standard asthma assessment tools provide limited insight as to underlying AHR.
- Tests such as forced expiratory volume in 1 second (FEV₁) reversibility are only indirectly associated with airway inflammation.

© AstraZeneca

34

Why is FeNO important in asthma management

- Exhaled NO levels increase during allergic inflammation and often correlate with eosinophilic inflammation (T2).
- FeNO levels are significantly higher in patients with allergic asthma compared with patients with nonallergic asthma.




35

35

Why is FeNO important in asthma management

Dweik, RA, Boggs, PB., Erzurum, S.C. et al. ATS Clinical Practice Guidelines: Interpretation of Exhaled Nitric Oxide Levels for Clinical Application - 2011

- "Patients with asthma have high levels of NO in their exhaled breath..."
- "Exhaled NO may be regarded as an indirect marker for up-regulation of airway inflammation"
- "Serial FENO levels increase progressively in response to allergen exposure and the advent of airway symptoms."




36

36

Why is FeNO important in asthma management

Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, Sklepko R, Szmitkowski M. Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naive asthma patients. - 2006

- Evaluate FeNO in a steroid-naive asthmatics and assess this measure with the results of other tests used in the diagnosis of asthma and monitoring of anti-inflammatory treatment in asthmatic patients.
- 101 steroid-naive asthmatics (56 allergic and 45 nonallergic) and 39 healthy volunteers
- Patients underwent measurement of FeNO, skin prick tests with common inhaled allergens, analysis of serum eosinophil cationic protein (ECP) and blood eosinophilia, and flow-volume spirometry
- Compared to the healthy volunteers, FeNO was elevated in both groups of asthmatics. FeNO in the allergic asthma group was higher than in the group of nonallergic asthmatics.




37

37

Why is FeNO important in asthma management

FeNO is a Predictor of ICS Response

- Low-dose inhaled corticosteroids (ICS) are the preferred first-line controller medication for the majority of patients with asthma.
- FeNO has the ability to identify patients who are likely to respond to ICS therapy.




38

38

Why is FeNO important in asthma management

Smith and colleagues (2005)

- The study included 52 patients who were referred to a pulmonary function laboratory for evaluation of persistent, previously undiagnosed respiratory symptoms. After completing baseline testing, the patients had a 4-week trial of ICS therapy preceded by a placebo control phase. A steroid response was defined as a change in symptoms, peak flows, spirometry, or airway hyperresponsiveness to adenosine.
- Using a FeNO threshold value greater than 47 ppb was found to be highly indicative of corticosteroid responsiveness. The predictive accuracy of FeNO to identify steroid responses was significantly greater than the predictive accuracy of conventional predictors, including FEV₁.




39

39

Question 6

FeNO measurements can help identify

- A. ICS adherence
- B. Nonadherence to ICS
- C. Uncontrolled inflammation
- D. All of the above




40

40

Why is FeNO important in asthma management



Aaron, Choy, Scheerens, et al. (2013)

- Studied various mediators of Type 2 inflammation (IL-13, IL-5, IgE) and the efficacy of targeted pathway therapies
- 3 noninvasive biomarkers were found to be promising
 - FeNO
 - Serum periostin
 - Blood eosinophils




45

FeNO & Guidelines





46

Expert Panel Report 4 – Guidelines for the Diagnosis and Management of Asthma (NIH)



- Emphasized the importance of asthma control
- Control must be monitored on a periodic basis to determine whether therapy should be maintained or adjusted (up/down)
- Recommend stepwise approach to controlling asthma (SABA then ICS...)
- Emphasized importance of assessing patient adherence, inhaler technique and environmental control measures
- Minimally invasive markers (biomarkers) such as fractionated exhaled nitric oxide and sputum eosinophils may be useful, but biomarkers require further evaluation before they can be recommended as clinical tools for routine management.




47

NIH – Asthma Management Guidelines 2020

- ➔ FeNO measurement may support a diagnosis of asthma in individuals where a diagnosis is uncertain after complete H&P, and spirometry with bronchodilator
- ➔ FeNO may be used as part of ongoing monitoring and management when there is uncertainty in adjusting therapy using clinical and laboratory assessment
- ➔ FeNO should not be used in isolation to assess control, predict future exacerbations, or assess severity of exacerbation
- ➔ Pediatric patients < 4 y/o with recurrent episodes of wheezing, FeNO does not predict the future asthma.


48

48




ATS Clinical Practice Guidelines 2021

- Asked - Should patients with asthma in whom treatment is being contemplated undergo FeNO testing?
- Assessment of FeNO in the clinic may be complementary to other assessment tools, particularly if there is evidence that the use of FeNO-based care improves specific outcomes that reflect asthma control

 © 2021 AbbVie Inc. All rights reserved.


49

49




ATS Clinical Practice Guidelines 2021

- FeNO correlates well with airway inflammation measured in induced sputum, providing a noninvasive way to assess T2 AHR in asthma
- Treatment with ICSs results in a marked decrease in a subset of patients with ongoing inflammation

 © 2021 AbbVie Inc. All rights reserved.

50

50




ATS Clinical Practice Guidelines 2021

- Although FeNO levels do not correlate well with the degree of baseline airflow obstruction, they tend to correlate well with the severity and features of "indirect" or "endogenous" AHR, such as exercise-induced bronchoconstriction
- Interestingly, FeNO levels change dynamically after bronchoprovocation with an initial decrease during airway narrowing followed by an increase as the airways dilate after the nadir during the late airway response.

Abbott

51



ACAAI/AAAAI Joint Statement


- The measurement of FeNO is quick, simple and reproducible, and has been standardized for clinical use.
- The measurement of inflammation, using FeNO, is a paradigm change in the diagnosis and management of asthma.

52

Global Initiative for Asthma (GINA) 2024

FeNO in Diagnosis:

- Modestly associate with blood and sputum eosinophilia
- Higher in Th2 inflammation, as often seen in asthma BUT also elevated for non-asthma conditions
- Not always elevated in asthma
- Lower in smokers
- Lower during bronchoconstriction and early allergic response
- Levels may be lower OR higher during a viral infection




53

Global Initiative for Asthma (GINA) 2024

FeNO in Management:

- Main role to help guide treatment decisions in patient with severe asthma



54

National Institute for Health and Care Excellence (NICE) Guidelines (UK) 2024

1.2 Objective tests for diagnosing asthma in adults, young people and children aged 5 to 16 with a history suggestive of asthma

Children 5-16

- 1.2.5 Measure the FeNO level in children with a history suggestive of asthma.
- Diagnose asthma if the FeNO level is 35 ppb or more.

55

NICE, BTS, SIGN Collaboration 2024

Adults

- 1.2.1 Measure the blood eosinophil count or fractional exhaled nitric oxide (FeNO) level in adults with a history suggestive of asthma. Diagnose asthma if the eosinophil count is above the laboratory reference range or the FeNO level is 50 ppb or more.

Monitoring Adults

- 1.5.4 Consider fractional exhaled nitric oxide (FeNO) monitoring for adults with asthma:
At their regular review, and before and after changing their asthma therapy.


56

Summary

FeNO measuring and tracking benefits asthma patients during:

Diagnosis
Identify & assess current level of airway inflammation

Management
Identify patient's likelihood of corticosteroids responsiveness
Optimize adherence to corticosteroids treatment to aid in reducing exacerbations
Determine biological therapy as indicated



57

57

Thank you!


Questions?

Contact Methapharm Respiratory

education@methapharm.com
hmurgatroyd@methapharm.com

1.800.287.7686

www.methapharmrespiratory.com




58

58

References

- AAAAI/ACAAI Joint Statement of Support of the ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide for Clinical Applications. February 1, 2012
- An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (F E 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. American Journal of Respiratory and Critical Care Medicine Volume 184, Issue 5.
- Arron JR, Choy DF, Scheerens H, Matthews JG. Noninvasive biomarkers that predict treatment benefit from biologic therapies in asthma. Ann Am Thorac Soc. 2013 Dec;10 Suppl:S206-13. doi: 10.1513/AnnalsATS.201303-047AW. PMID: 24313774.
- Asthma: diagnosis, monitoring and chronic asthma management (BTS, NICE, SIGN) NICE guideline Published: 27 November 2024 www.nice.org.uk/guidance/ng246
- Donohue JF, Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. Respir Med. 2013 Jul;107(7):943-52. doi: 10.1016/j.rmed.2013.02.018. Epub 2013 Apr 17. PMID: 23601567.



59

59

References

- Fajt, M.L., and Wenzel, S.E. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. *J Allergy Clin Immunol*. February 2015.
- Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention, 2024*. Updated May 2024. Available from www.ginaasthma.org
- Louis R, Satali I, Ojanguren I, et al. European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults. *Eur Respir J* 2022
- Marie 'lle W, Pijnenburg, E, Marije Bakker, Wim C. Hop, and Johan C. De Jongste. Titrating Steroids on Exhaled Nitric Oxide in Children with Asthma A Randomized Controlled Trial. *Am J Respir Crit Care Med* Vol 172. pp 831-836, 2005
- Smith A.D., Cowan J.O, Brassett K.P. et al. Exhaled Nitric Oxide A Predictor of Steroid Response. *Am J Respir Crit Care Med* Vol 172. pp 453-459, 2005
- Syk J, Malinovsky A, Johansson G, Uden A, Andreasson A, Lekander M, Alving K. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial. *JACI: In Practice*. Published online 11 October 2013



60

60

References

- Svenningsen S, Nair P. Asthma Endotypes and an Overview of Targeted Therapy for Asthma. *Front Med (Lausanne)*. 2017 Sep 26;4:158. doi: 10.3389/fmed.2017.00158. PMID: 29018800; PMCID: PMC5622943.
- Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma An Official American Thoracic Society Clinical Practice Guideline Sumita B, Khatri, Jonathan M, Iaccarino, Amisha Barochia, Israa Sophie, Praveen Akuthota, Anna Brady, Ronina A. Covar, Jason S. Debley, Zuzana Diamant, Anne M. Fitzpatrick, David A. Kaminsky, Nicholas J. Kamyon, Sandhya Khurana, Brian J. Lipworth, Kevin McCarthy, Michael Peters, Loretta G. Quie, Kristina R. Roes, Elena K. Schneider-Futschik, Christine A. Sorinnes, and Teri S. Hallstrand; on behalf of the American Thoracic Society Assembly on Allergy, Immunology, and Inflammation *Am J Respir Crit Care Med* Vol 204, Iss 10, pp e97-e109, Nov 15, 2021
- Wang Z, Pianosi P, Keogh K, Zaiem F, Alsawas M, Alahdab F, Almasri J, Mohammed K, Larrea-Mantilla L, Farah W, Darsz L, Barriounevo P, Guinji S, Prokop LJ, Murad MH. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Dec. Report No.: 17(18)-EHC030-EF. PMID: 29533572.
- Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, Skieplko R, Szmittkowski M. Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naïve asthma patients. *J Investig Allergol Clin Immunol*. 2006;16(4):239-46. PMID: 16889281.



61

61
