Clinical Benefits of FeNO Monitoring in Asthma

RYAN BURTON, MS, RPFT

Disclosures

I am an employee of Circassia Pharmaceuticals.

Objectives

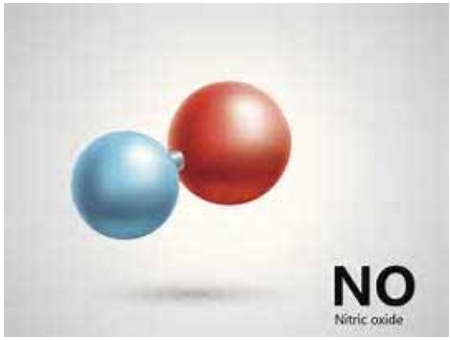
- Nitric Oxide
- Inflammation in Asthma
- Phenotyping Personalized Medicine
- Aids in the diagnosis of th2 allergic inflammation
- Instrument for optimizing the dose of inhaled corticosteroids (ICS)
- Non-Adherence to medication (ICS) / Improper Medication Technique
- Outcomes Data
- Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic
- Clinical Utility of FeNO testing

Fractional Exhaled Nitric Oxide – (FeNO)

NITRIC OXIDE

What is Nitric Oxide (NO) ?

- NO is present in virtually all mammalian organ systems, including the human lung
- Present in the exhaled breath of all humans
- NO is recognized to play key roles in virtually all aspects of lung biology and has been implicated in the pathophysiology of lung diseases, including asthma
- The functions and effects of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator
  - Neonatal respiratory distress syndrome
  - Health/Fitness supplements



2011 ATS FeNO Guidelines on Interpretation

Fractional Exhaled Nitric Oxide – (FeNO)

ASTHMA AND INFLAMMATION

Asthma Facts

- Asthma cost the US $56 Billion dollars a year****
- 1 in 11 children have asthma*
- 1 in 12 adults have asthma*
- 1 in 5 children with asthma went to an emergency department for asthma-related care***
- 479,000 hospitalizations a year****
- 1.6 million emergency room visits a year w/asthma as primary diagnosis **
- 10.5 million physician office visits a year w/asthma as primary diagnosis***

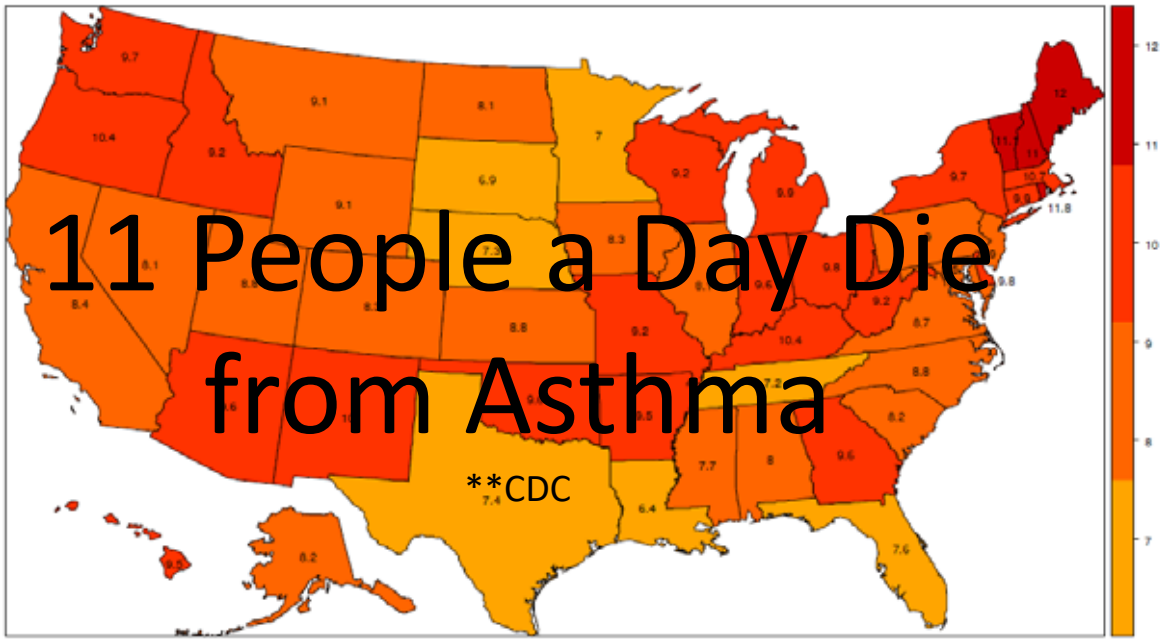
$80 Billion Dollars!

Annals of ATS 2017

Source: U.S. Centers for Disease Control and Prevention

* 2010, ** 2013, *** 2012, **** 2009

Figure 4: Asthma - Current Adult Prevalence (%) by State, 2011



Source: BRFSS 2011.

Note: Due to significant methodology changes in 2011 to the survey used to obtain these data, comparisons with previous years are not advisable.

Asthma Heterogeneity

- Complex genetic disorder with heterogeneous phenotype
  - Largely attributed to interactions among many genes and between these genes and the environment
- **Variability in underlying inflammation**, clinical symptoms, natural history, and response to treatment
  - Variability contributes to suboptimal diagnosis and therapeutic control
  - Environment
  - Access to healthcare
  - Specialists vs primary care
  - Co-morbidities

1. Hakonarson et al. Am J Pharmacogenomics. 2002;2(3):155-166. 2. Lötvall et al. J Allergy Clin Immunol. 2011;127(2):355-360. 3. Dolovich et al. Thorax. 1981;36(9):614-644.

Inflammation in Asthma

NHLBI, EPR 3, 2007

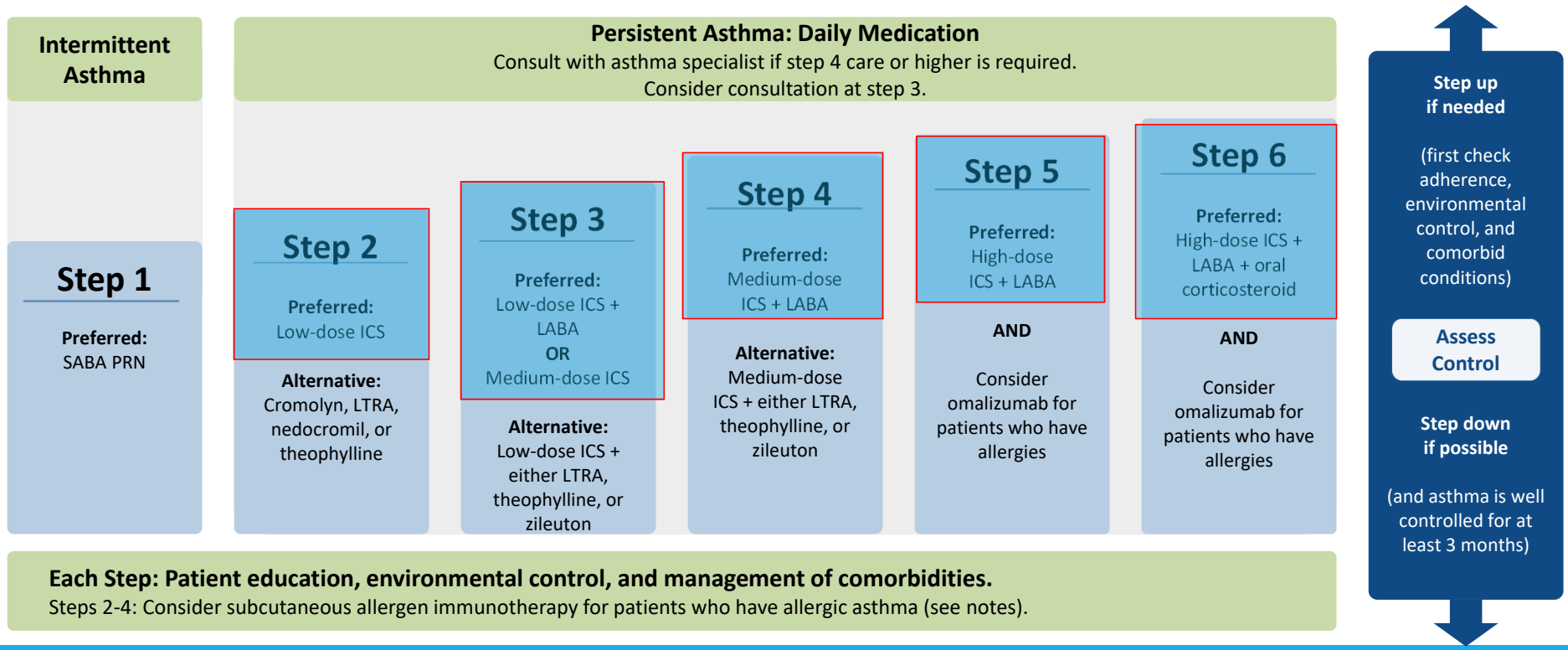
Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and **underlying inflammation**.

National Heart Lung and Blood Institute
People Science Health

GINA - 2017

Asthma is a **chronic inflammatory disorder** of the airways in which many cells and cellular elements play a role. The **chronic inflammation** is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing…

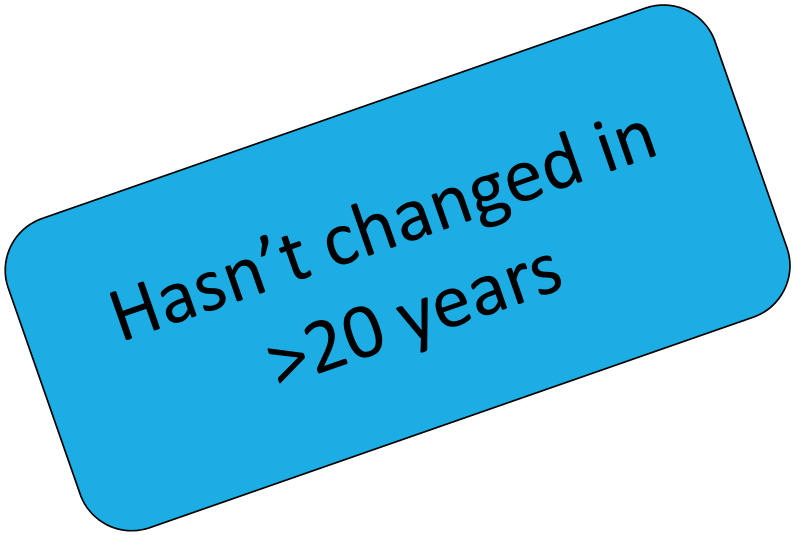
Guideline Recommendations for Stepwise Treatment of Asthma



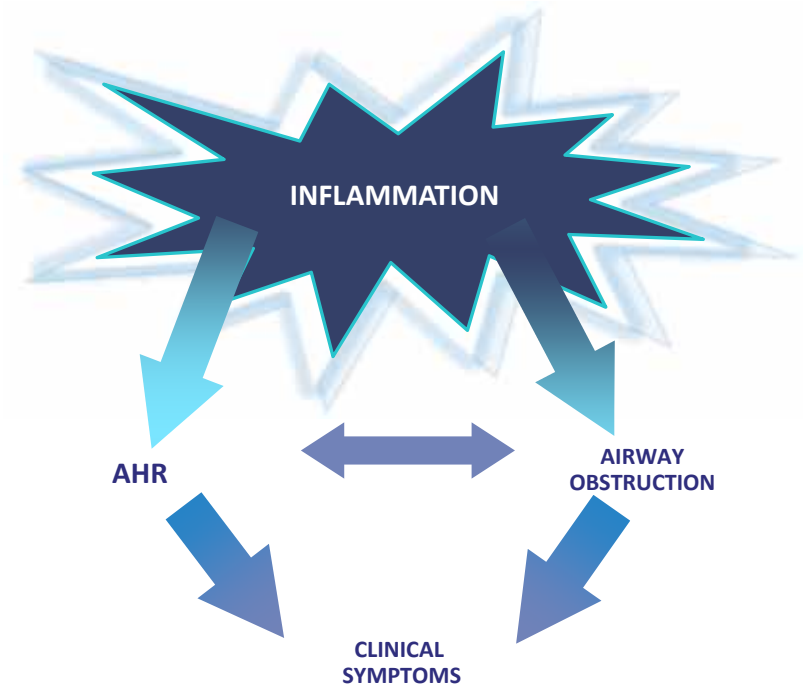
Quick-relief Medication for All Patients •SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed •Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment

Current Assessment of Asthma Management

- Assessment of symptoms / history
- Assessment of lung function
- Assessment of AHR
- Symptoms are not predictive of response to ICS
- Lung function can be misleading, especially in children
  - Quality control is a major issue
  - Lung function can be normal in patients with severe asthma
- Measurement of AHR
  - Expensive
  - Technically difficult
  - Non-specific



Tools Used in the Clinical Assessment of Asthma

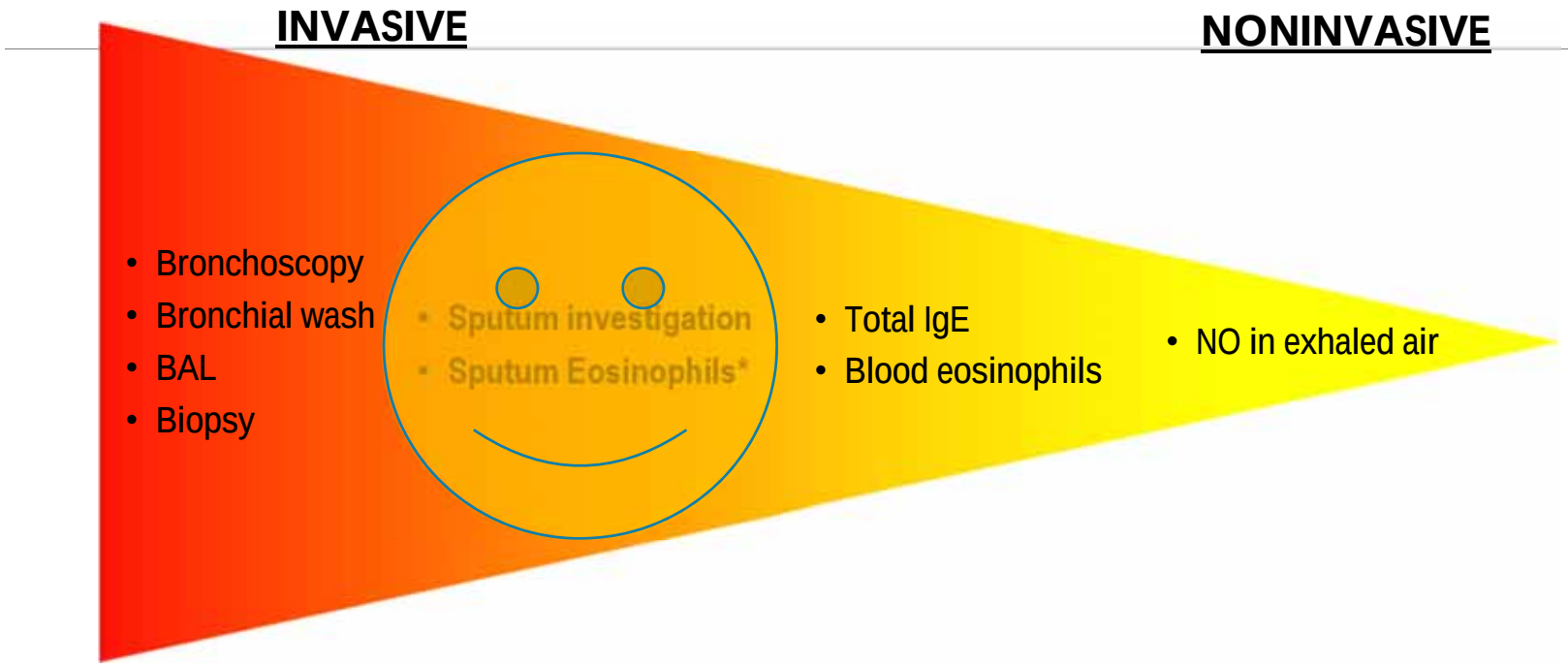


Clinical Symptoms: *ACT, AQLQ, etc*

Airway Hyperresponsiveness (AHR): *Bronchodilator testing, Methacholine challenge, etc*

Airway Obstruction: *Spirometry, PEF, etc*

Tools to Assess Inflammation



BAL, bronchoalveolar lavage; NO, nitric oxide.

Goal of Therapy: Control of Asthma

Reduce Impairment

- **Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion).**
- Require infrequent use (≤2 days a week) of inhaled SABA for quick relief of symptoms (not including prevention of exercise-induced bronchospasm [EIB]).
- Maintain (near) normal pulmonary function.
- Maintain normal activity levels (including exercise and other physical activity and attendance at school or work).
- Meet patients' and families' expectations of and satisfaction with asthma care.

Reduce Risk

- **Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations.**
- Prevent loss of lung function; for children, prevent reduced lung growth.
- **Provide optimal pharmacotherapy with minimal or no adverse effects of therapy.**

ADAPTED FROM NHLBI EPR3 2007

Fractional Exhaled Nitric Oxide – (FeNO)

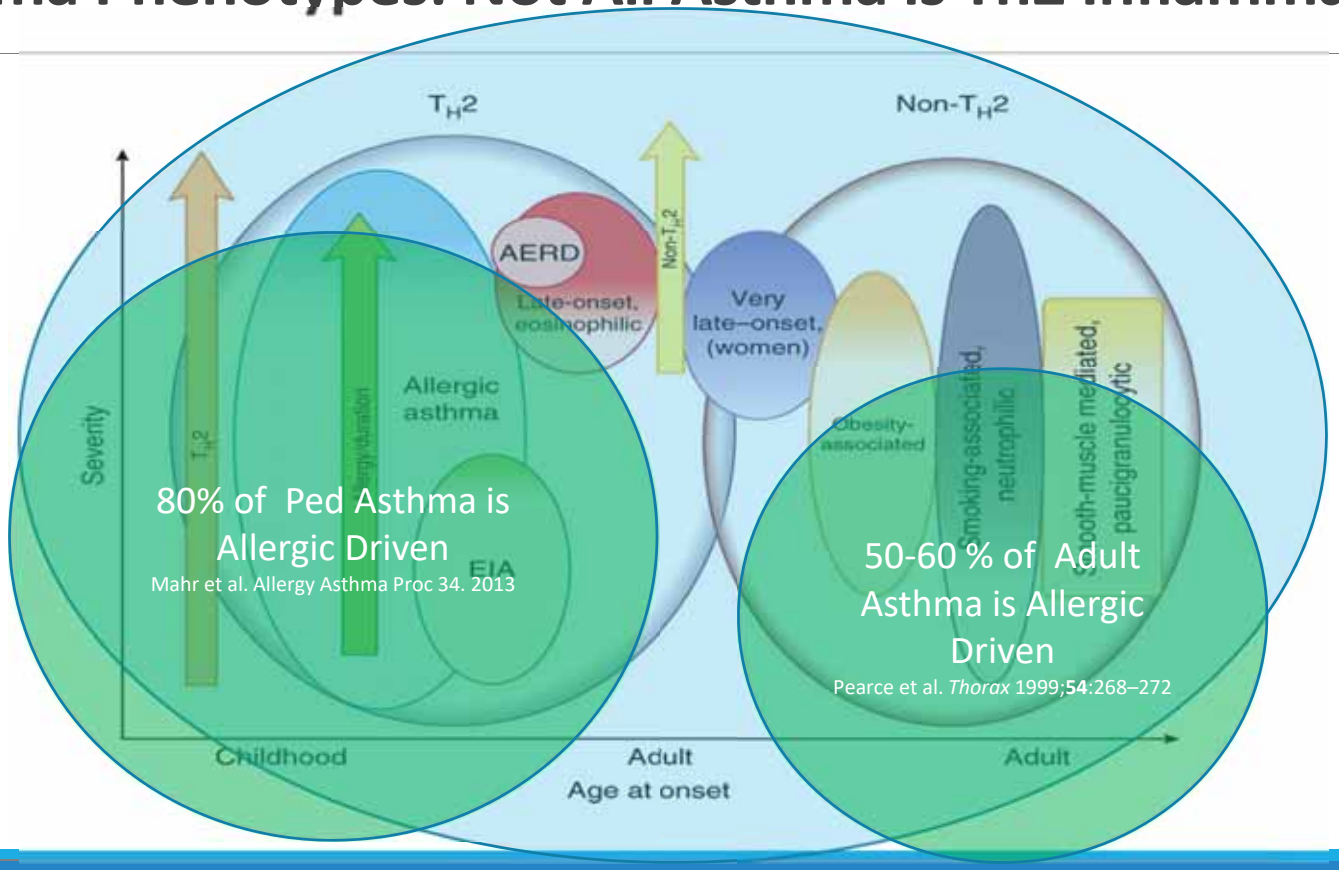
PHENOTYPING/PERSONALIZED MEDICINE

Cluster Phenotyping By Degree Of Th2 Inflammation

- Two distinct molecular phenotypes:
  - Therapy targeting Th2 cytokines only benefits Th2-driven phenotypes
  - Non-Th2-driven asthma does not respond well to current therapies including ICS

Woodruff PG, et al. *Am J Respir Crit Care Med*. 2009;180(5):388-395

Asthma Phenotypes: Not All Asthma is Th2 Inflammation!



80% of Ped Asthma is Allergic Driven

Mahr et al. Allergy Asthma Proc 34. 2013

50-60 % of Adult Asthma is Allergic Driven

Pearce et al. *Thorax* 1999;**54**:268–272

Wenzel S Nat Med 2012

Asthma Inflammation and Pathophysiology

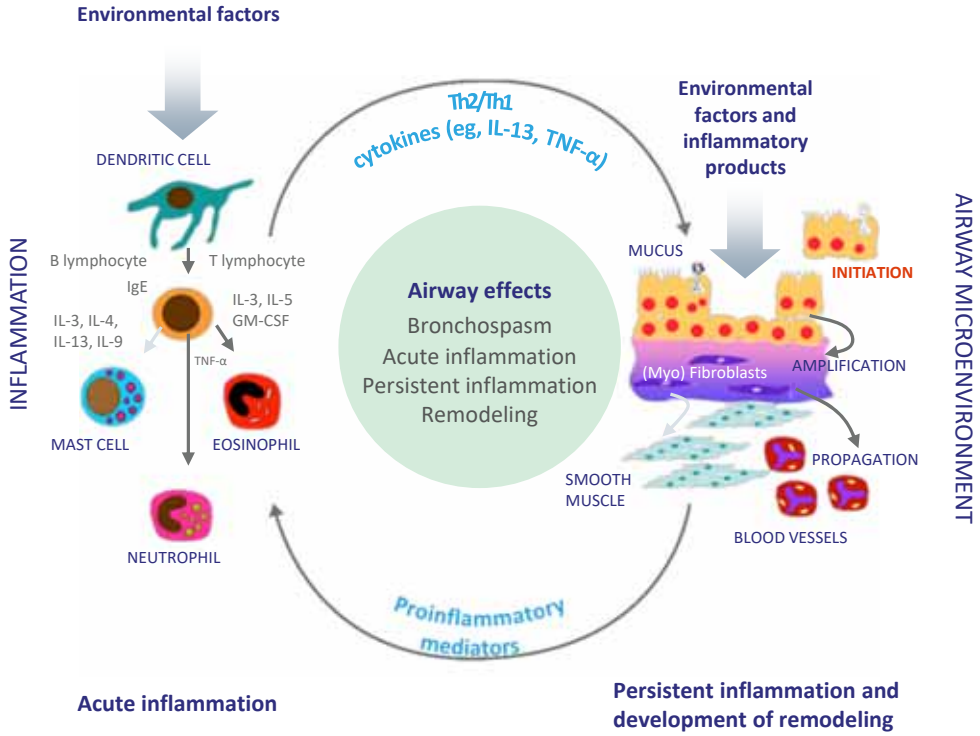
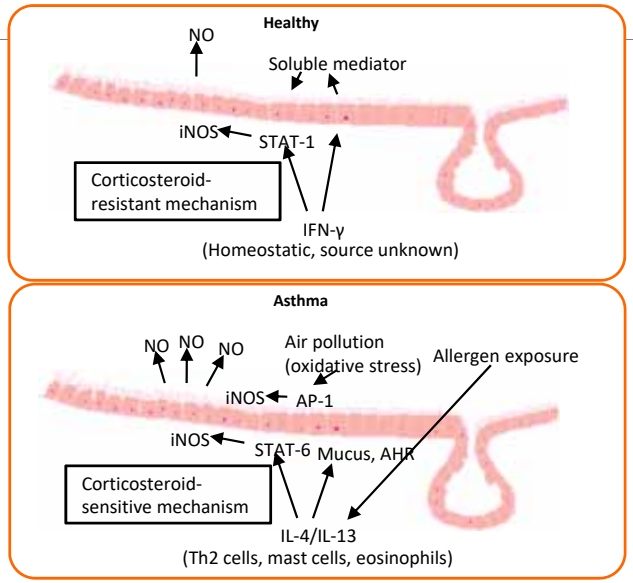


Figure adapted and reprinted from The Lancet, 368, Holgate et al, The mechanisms, diagnosis, and management of severe asthma in adults, 780-793. Copyright 2006, with permission from Elsevier. AHR, airway hyperresponsiveness; GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL, interleukin; TNF-α, tumor necrosis factor alpha. Expert Panel Report 3. National Heart, Lung, and Blood Institute. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 12, 2011.

Nitric Oxide (NO) Production

- NO endogenous regulatory molecule
- Synthesis regulated by family of enzymes—NO synthases (NOS)
- Inducible NOS-derived NO is predominantly produced in bronchial wall epithelial cells
- Exhaled NO levels increase during Th2 (allergic) inflammation—often correlate with eosinophilic inflammation



AP, activator protein; iNOS, inducible nitric oxide synthase; IL, interleukin; IFN-γ, interferon-gamma; STAT, signal transducer and activator of transcription. 1. Yates. Immunol Cell Biol. 2001;79(2):178-190. 2. Alving et al. Eur Respir Mon. 2010;49:1-31.

Fractional Exhaled Nitric Oxide – (FeNO)

AIDS IN THE DIAGNOSIS OF TH2 ALLERGIC INFLAMMATION

Elevated FeNO Distinguishes Asthma From Other Allergic Conditions

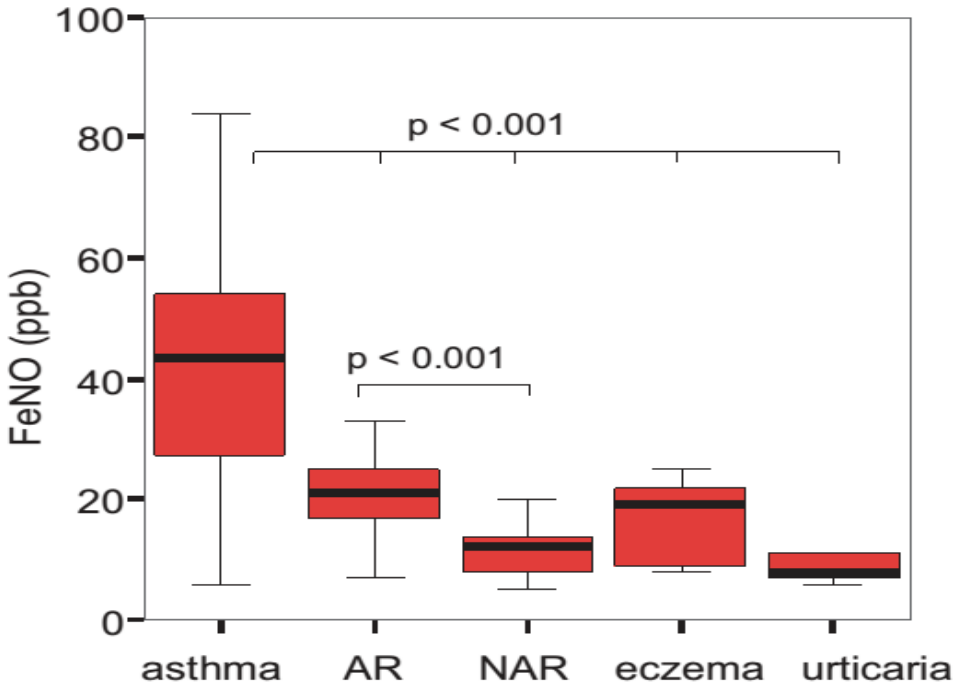
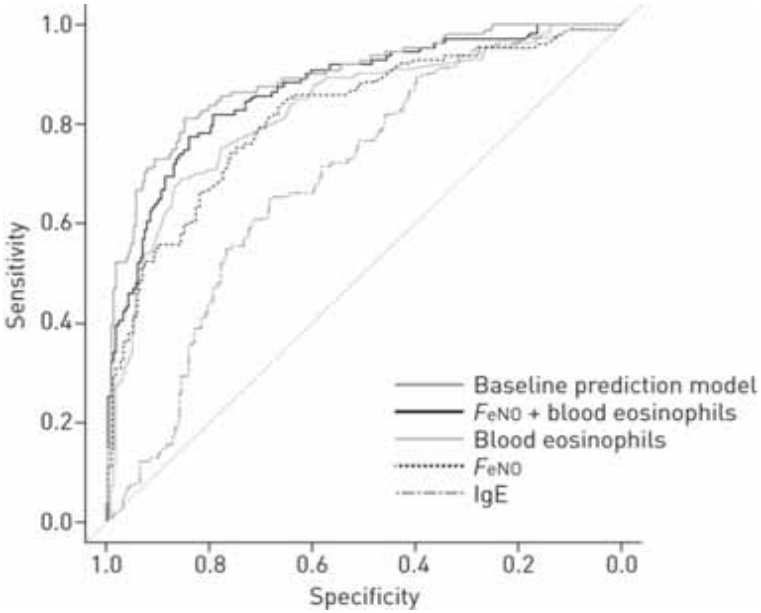


Figure from Cordeiro et al. With permission. AR, allergic rhinitis; NAR, nonallergic rhinitis; Cordeiro et al. Allergy Asthma Proc. 2011;32(2):119-126.

Diagnostic Accuracy of FeNO, Blood Eosinophils, Total IgE And Their Combinations To Identify Sputum Eosinophils

ROC Characteristics for FeNO, Blood Eosinophils, IgE and combinations



Westerhof et al. *Eur Respir J*. 2015;46(3):688-696.

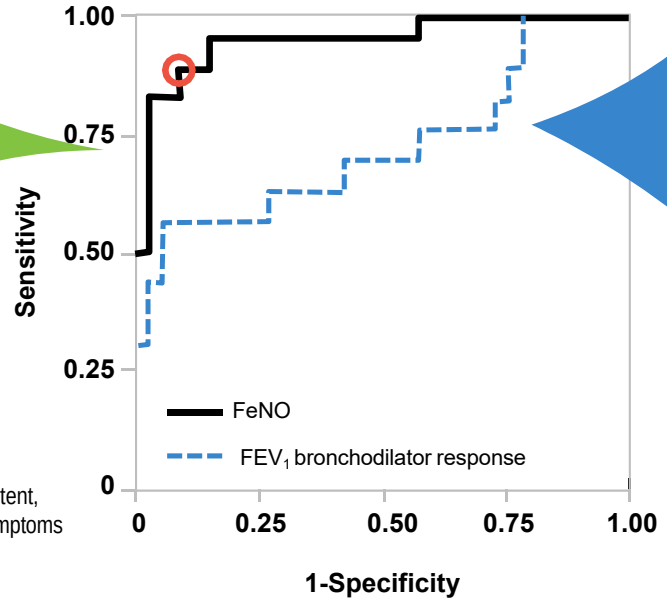
Fractional Exhaled Nitric Oxide – (FeNO)

INSTRUMENT FOR OPTIMIZING THE DOSE OF INHALED CORTICOSTEROIDS (ICS)

Significantly Better Than FEV$_1$

FeNO Measurement Predicts ICS Responsiveness

In patients with nonspecific symptoms, a FeNO value of > 47 ppb is highy indicative of corticosteriod responsiveness



FeNO measurement was significantly better than FEV_1, bronchodilator for predicting response to inhaled fluticasone propionate ($P < 0.01$)

52 patients referred by their family practitioners to the hospital with persistent, previously undiagnosed respiratory symptoms

Smith et al. Am J Respir Crit Care Med. 2005;172(4):453-459..

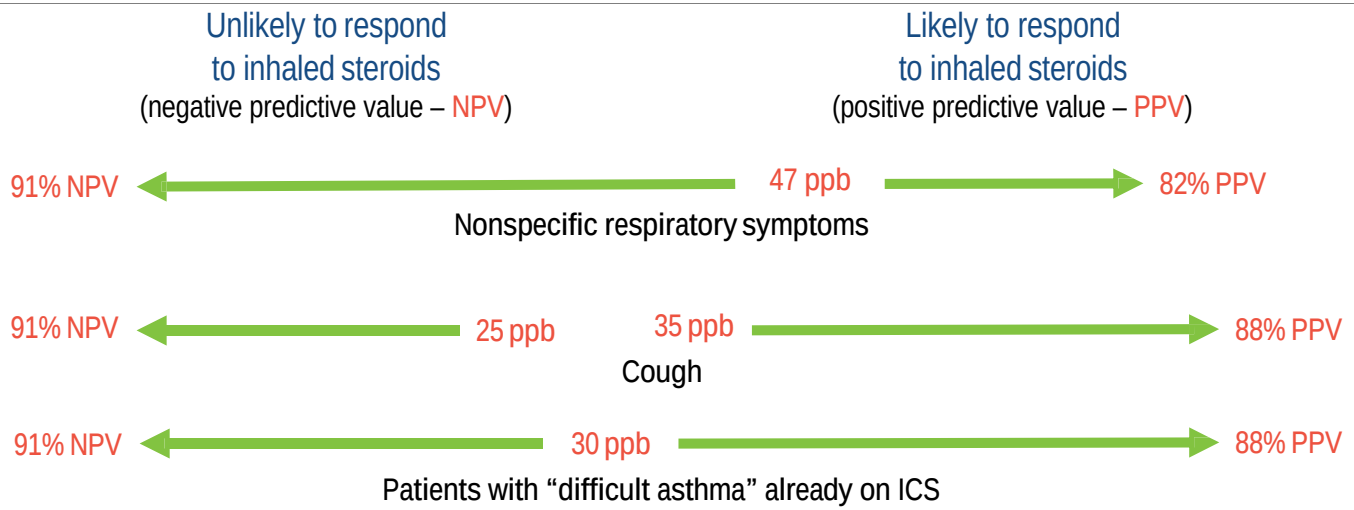
FeNO Testing to Support an Asthma Diagnosis

Parameter*	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Peak flow improvement with steroid >15%	24	100	100	69
FEV_1 improvement with steroid >15%	12	100	100	66
FEV_1 <80% predicted	29	100	100	71
FEV_1/FVC <70%	35	100	100	73
Sputum eosinophils >3%	86	88	80	92
FeNO >20 ppb	88	79	70	92

- Bronchodilator reversibility and/or AHR was used to establish asthma diagnosis in study (47 patients with symptoms suggestive of asthma, 17 were subsequently diagnosed with asthma)
- Both FeNO and sputum eosinophils had significantly higher diagnostic accuracy than lung function tests
- FeNO testing provides added advantage of being noninvasive and easy to perform

Smith et al. *Am J Respir Crit Care Med*. 2004;169(4):473-478.

Exhaled NO Identifies Steroid Responsiveness



FeNO measurements provide the physician with means of evaluating asthma patients' response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. Not all patients with asthma will have an elevated FeNO level. FeNO levels should be interpreted in the clinical context

Smith et al. *Am J Respir Crit Care Med*. 2005;172(4):453-459.

Fractional Exhaled Nitric Oxide – (FeNO)

NON-ADHERENCE/TECHNIQUE TO MEDICATION (ICS)

Lack of Improvement in Medication Adherence in Asthma

- Adherence improvement strategies have included patient education, motivational interviewing, adherence feedback, provider communication skill training, and use of mobile communication technology.
- Collectively, most interventions had a positive but modest impact on adherence that was not sustainable long term.
- A sample of 9 studies conducted between 1996 and 2015 using objective measures of adherence indicate no overall change in adherence rates over 2 decades

Author	Year	Mean % adherence
Milgrom et al[16]	1996	40
Chung and Naya[17]	2000	64
Jonasson et al[18]	2000	46.9
Bender et al[1]	2000	52
McQuaid et al[19]	2003	48
Walders et al[20]	2005	46
Bender et al[21]	2007	47
Krishnan et al[22]	2012	58
Mosnaim et al[23]	2015	19
Bender et al[24]	2015	36

Bender, JACI Pract 2016

Asthma Patients do not Use Medication Inhalers Correctly

- High prevalence (90%) of inhaler technique errors (>1 error) across all devices.
- More than 20% of the patients demonstrated at least 4 errors when using their controller inhalers.

TABLE II. The 12 most common DPI Diskus errors recorded in the iHARP study[22]

1. Did not slide cover fully open
2. Dose lost after preparation because of holding downward
3. Shook inhaler device after dose preparation
4. Did not breathe out to empty lungs
5. Exhaled into the inhaler before inhalation
6. Did not put Diskus in mouth and seal lips around mouthpiece
7. Did not have head tilted such that chin is slightly upward
8. Insufficient inhalation effort (inhalation is not fast, forceful from the start, and as long as possible)
9. Did not inhale through mouth
10. No breath-hold follow inhalation (or holds breath for <3 s)
11. Patient had expired inhaler or empty inhaler
12. After inhalation did not replace cover

Braido, JACI IP 2016

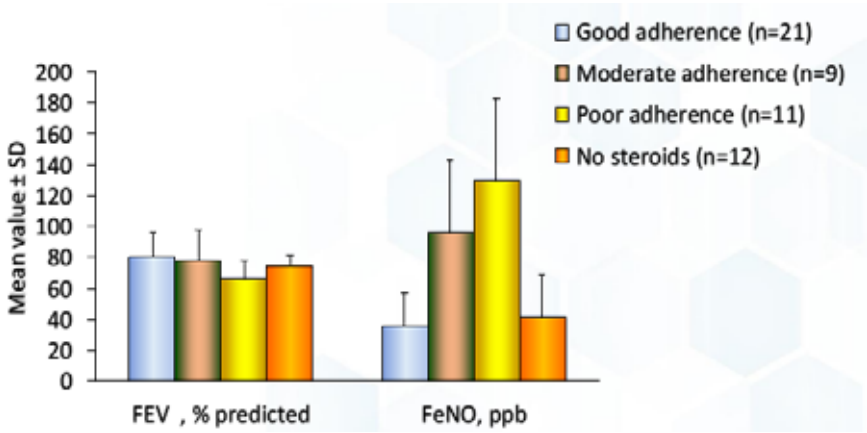
Percent of Correct, Acceptable, Poor Inhaler Tests

Correct or acceptable inhaler technique over course of 40 years has remained below 50%

Sanchis et al CHEST 2016

FeNO but Not FEV_1 Was Associated with ICS Non-Adherence

- Patients followed for 2.5yrs; total of 53 visits
- Mean FeNO levels were significantly reduced in patients with good ICS adherence
- FEV_1 levels were not substantially different among adherence groups
- Adherence determined by calculating number of doses taken per day/doses prescribed x 100. Good, moderate, and poor adherence defined as >75% adherence, 50% to 75% adherence, or <50% adherence to prescribed medication, respectively.



Delgado-Corcoran et al. Pediatr Crit Care Med. 2004;5(1):48-52.

Fractional Exhaled Nitric Oxide – (FeNO)

OUTCOMES DATA

Cochrane: FeNO-based Management Reduces Exacerbation Rates

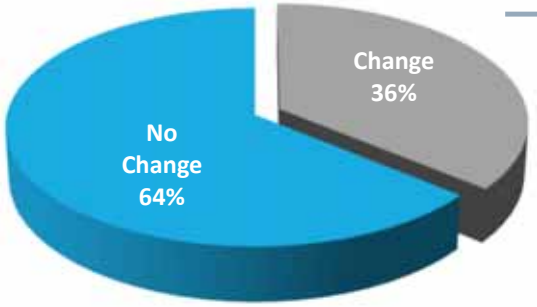
Population	Meta-Analysis Design	Odds Ratio for Reducing Exacerbations Using FeNO vs. Symptoms-based Approach
Adult[1]	7 Studies, 1700 Randomized Subjects, 1546 Completed Study	OR 0.60 (95% CI 0.43-0.84); NNTB in one year = 12 (95% CI 8-32)
Pediatric[2]	9 Studies , 1426 Randomized Subjects, 1370 Completed Study	OR 0.63 (95% CI 0.49-0.83)

- Conclusions: Tailoring asthma medications based on FeNO levels (compared with primarily on clinical symptoms) decreases the frequency of asthma exacerbations.
- The rate of exacerbations (number of exacerbations per 52 weeks) was significantly reduced by at least 40% by incorporating FeNO into asthma management.
- Number needed to treat to benefit (NNTB) over 52 weeks was clinically relevant and very low (12 in adults, 9 in children)

1. *Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011440. 2. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD011439*

Real World Experience with Use of FeNO-LaForce Study

Treatment Changes Following FeNO Testing (N=50)



Treatment Change Details

Added Medication or Increased Medication Dose	Subtracted Medication or Decreased Medication Dose
10 (20%)	8 (16%)

- Treatment decision-making study to evaluate the impact of FeNO testing on asthma management (physician assessment of inflammation, dosing and cost savings)
- Treatment decisions were altered (step up, step down, add-on) in 36% of subjects when FeNO was used in conjunction with standard clinical assessment, ACT, and spirometry

LaForce et al Annals Allergy Asthma Immun 2014

Fractional Exhaled Nitric Oxide – (FeNO)

HELPS TO IDENTIFY ASTHMATICS WHO ARE POSSIBLE CANDIDATES FOR TREATMENT WITH A BIOLOGIC

Severe Asthma vs Difficult to Control Asthma

Severe refractory asthma is characterized by difficulty to achieve disease control despite high dose inhaled steroids plus long acting beta agonists (LABAs) or oral corticosteroids (OCS).

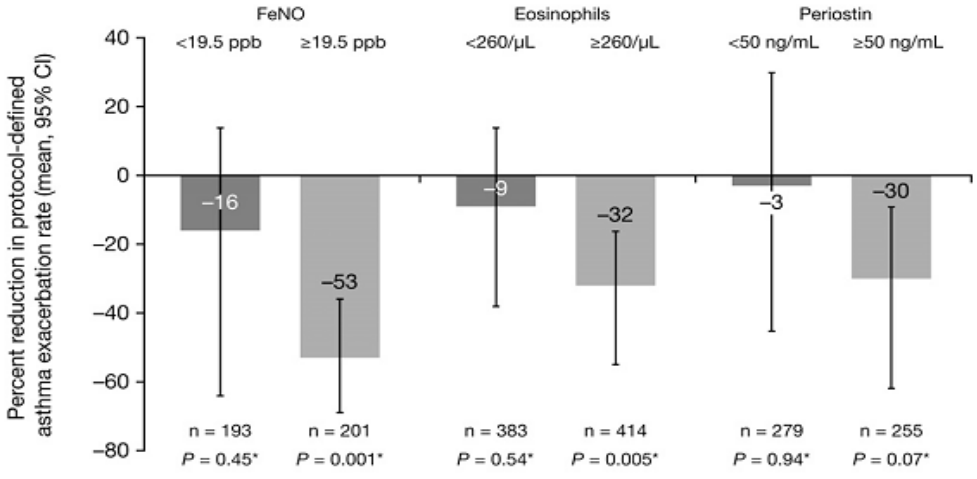
Difficult to control asthma can be attributed to factors other than asthma itself such as: Non adherence, Poor inhaler technique, Comorbidities

- **5 - 10%** of 26 million Americans suffering from asthma experience severe disease
- Approximately **1/2 of direct asthma costs** related to care of patients with severe disease ($56 billion total, $28 billion for severe asthma)
- Patients with uncontrolled severe asthma incur up to 3x cost compared to controlled severe asthma ($21 billion)
- Pharmaceuticals represent the single largest expenditure for asthma care

Hankin CS et al. *J Allergy Clin Immunol* 2013; 131s: AB126.

Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic

- A small minority of asthma patients cannot achieve control of their disease with traditional therapies and are considered for treatment with biologic therapy. [1]
- Decision making in these patients is difficult; FeNO helps to confirm ICS failures, non-adherence/compliance and identifies patients that have persistent airway inflammation despite optimization on current therapy.
- Baseline measurement of FeNO identifies patients with persistent inflammation and who will benefit most from a biologic such as omalizumab. [2]
- FeNO identifies patients likely (and unlikely) to respond to Xolair® (omalizumab)[2]



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

1. Hekking et al, J Allergy Clin Immunol 2015;135:896-902. 2.Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma. Am J Respir Crit Care Med. 2013;187(8):804-811. Mean percent reduction (95% CI) in protocol-defined asthma exacerbation rate in the low- and high-biomarker subgroups (baseline fractional exhaled nitric oxide [FeNO], peripheral blood eosinophils, and serum periostin).*Exacerbation reduction P values; omalizumab versus placebo in each biomarker subgroup.

Fractional Exhaled Nitric Oxide – (FeNO)

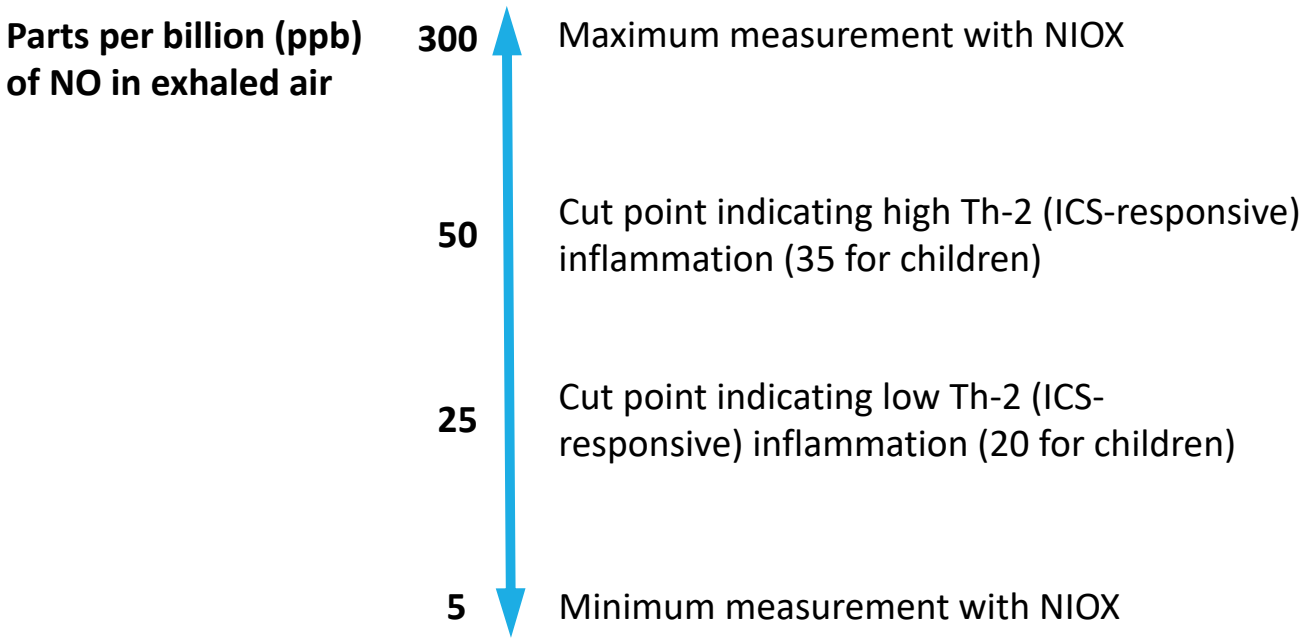
CLINICAL UTILITY OF FENO TESTING

Clinical Interpretation of FeNO Measurements (2011 ATS)

- Use of cut points rather than reference values
- Account for age as a factor in children <12 years old
- Clinical context in which FeNO is obtained should be taken into account and reported*
- When monitoring patients, clinically significant increase determined as
  - >20% significant change for levels >50 ppb
  - >10 ppb significant change for levels <50 ppb
- Decrease of >20% in an elevated FeNO level, which often occurs 2 to 6 weeks after initiation of anti-inflammatory therapy, supports that treatment was successful for reduction of inflammation

**Includes date, time of day, age, sex, ethnicity, height, weight, smoking status, reasons for test, prior diagnosis if known, whether patient was using ICS or oral steroids at time of testing, and number of measurements made. Dweik et al. Am J Respir Crit Care Med. 2011;184(5):602-615.*

Clinical Guide to Interpretation of FeNO Levels and Airway Inflammation in Asthma



Dweik et al. *Am J Respir Crit Care Med.* 2011;184(5):602-615.

Additional Factors Affecting FeNO Levels

- Airway infection (viral)
- Allergic rhinitis
- Atopy
- Nitrate-rich diet
- Acute Bronchodilator

- Spirometric maneuvers that cause bronchospasm
- Smoking
- Acute Bronchoconstriction
- Alcohol consumption
- Exercise

Effects generally not clinically significant

1. *Sanders et al. J Allergy Clin Immunol. 2004;113(4):697-702.* ***2.*** *Henriksen et al. Eur Respir J. 1999;13(2):301-306.* ***3.*** *Olin et al. Respir Med. 2001;95(2):153-158.* ***4.*** *Papi et al. Am J Respir Crit Care Med. 2000;162(5):1773-1777.* ***5.*** *Silkoff et al. Am J Respir Crit Care Med. 1999;159:940-944.* ***6.*** *Terada et al. Am J Respir Crit Care Med. 2001;164:1879-1884.* ***7.*** *Yates et al. Eur Respir J. 1996;9(6):1130-1133.* ***8.*** *Piacentini et al. Thorax. 2002;57:771-773.* ***9.*** *Narang et al. Thorax. 2002;57(7):586-589.* ***10.*** *Kaneko et al. Am J Respir Crit Care Med. 1998;158(3):917-923.* ***11.*** *Verleden et al. Chest. 1999;116(1):59-64.* ***12.*** *Silkoff et al. J Allergy Clin Immunol. 2004;114(5):1241-1256.*

Effect of Drug Therapy on FeNO Levels

Drug Class	Effect on FeNO	Mechanism of Action
Corticosteroids	Marked Decrease	Less IL4/IL13 release Less STAT 6 Activation in epithelium Less iNOS Expression in epithelium
LTRA	Slight Decrease	Reduces eos Slight less IL13 release
Anti-IgE	Decrease	Blocks Th2/mast cell activation Less IL4/IL13 release
Anti IL4/IL13	Decrease	Reduces STAT 6 Activation in epithelium
Anti IL5	No Effect	
Anti TNF-x	No Effect	
Methylxanthines (theophylline, caffeine, etc)	No Effect	

Guideline Support

American Academy of Allergy Asthma & Immunology

American College of Allergy, Asthma & Immunology

American Thoracic Society Documents

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

Raed A. Dweik[1,2], Peter B. Boggs[3], Serpil C. Erzurum[1,2], Charles G. Irvin[4], Margaret W. Leigh[5], Jon O. Lundberg[6], Anna-Carin Olin[7], Alan L. Plummer[8], 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

Executive Summary
Introduction
Methods
Committee Composition, Meetings, and Document Preparation
Document Structure
Quality of Evidence and Strength of Recommendations
Why Should a FE_{NO} Test be Obtained?
Can FE_{NO} Be Used to Diagnose Asthma?
FE_{NO} Is Associated with Eosinophilic Airway Inflammation
FE_{NO} Predicts Likelihood of Corticosteroid Responsiveness
FE_{NO} Can Support a Diagnosis of Asthma
FE_{NO} May Predict AHR
Is There a Normal FE_{NO} Value?
Normal Values versus Relevant Cut Points for FE_{NO}
Confounding Factors that May Affect FE_{NO}
What Are the Clinically Significant Cut Points for FE_{NO}?
Low FE_{NO} (< 25 ppb in Adults; 20 ppb in Children)
High FE_{NO} (> 50 ppb in Adults, 35 ppb in Children)
Intermediate FE_{NO} (between 25 ppb and 50 ppb in Adults; 20–35 ppb in Children)
Persistently High FE_{NO} (> 50 ppb in adults, 35 ppb in Children)
Can FE_{NO} Be Used to Monitor Airway Inflammation?
Monitoring Airway Inflammation in Asthma
Minimally Important Differences, and Prognostic Significance of FE_{NO}
How Should a FE_{NO} Measurement Be Interpreted and Reported?
Other Situations in which FE_{NO} May Be Useful
COPD
Pulmonary Hypertension
Cystic Fibrosis and Nasal NO Measurements
Conclusions and Future Directions
Online Supplement
Appendix E1: Methods Checklist
Appendix E2: Technical Considerations and Sources of Variation in FE_{NO}
Appendix E3: Causes of High and Low FE_{NO} Levels
Appendix E4: Case Studies

This article has an online supplement, which is available from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 184, pp 602–615, 2011
DOI: 10.1164/rccm.9120115T
Internet address: www.atsjournals.org

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 a corticosteroid, and (4) prescreening of otherwise unexpected nonadherence to corticosteroid therapy.

Keywords: nitric oxide; asthma; inflammation; airway disease; exhaled breath; clinical applications

EXECUTIVE SUMMARY

Nitric oxide (NO) is now recognized as a biological mediator in animals and humans. NO is produced by the human lung and is present in the exhaled breath. It has been implicated in the pathophysiology of lung diseases, including asthma. The measurement of exhaled NO has been standardized for clinical use. Numerous studies have provided evidence regarding the applications of NO measurements in clinical practice, together with the performance characteristics and the strengths and the weaknesses of the test. Based on this evidence, this Clinical Practice Guideline is designed to guide clinicians as to how exhaled NO measurements should be used and interpreted.

EVIDENCE QUALITY AND RECOMMENDATIONS

These recommendations may vary with respect to the particular target population. Where this is the case, this has been included

RCCM9120115T_proof ■ 24-8-11 01:27:27

Guideline Support

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

Key Findings

1. Depending on the FeNO cutoff, the likelihood of having asthma in people ages 5 years and older increases by 2.8 to 7.0 times given a positive FeNO test result.
2. FeNO results can predict which patients will respond to inhaled corticosteroid therapy.
3. Using FeNO to manage long-term control medications including dose titration, weaning, and monitoring of adherence, reduces the frequency of exacerbations. https://www.ahrq.gov/

NICE National Institute for Health and Care Excellence

Initial treatment and objective tests for acute symptoms at presentation

1.1.5 Treat people immediately if they are acutely unwell at presentation, and perform objective tests for asthma (for example, fractional exhaled nitric oxide [FeNO], spirometry and peak flow variability) if the equipment is available and testing will not compromise treatment of the acute episode. https://www.nice.org.uk/

Summary

- Aids in the Diagnosis of Asthma and Identifies Patients with T2 Allergic Inflammatory Phenotype
- Instrument for Optimizing the Dose of Inhaled Corticosteroids (ICS)
- Uncovers Non Adherence to ICS
- Reduces the Likelihood of Exacerbations in Patients at Risk for Future Events
- Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic