Pulmonary Inflammation, Asthma, and Exhaled Nitric Oxide

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BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S The Lung Center

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Conflicts of Interest

None.

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Exhaled Breath Biomarkers

- Fraction of Exhaled Nitric Oxide (F_ENO)
- Exhaled Breath Condensate (EBC)
- Volatile organic compounds (VOCs)

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Non-Invasive Assessment of Disease

Airway Diseases

- Asthma
- Sinus disease
- COPD
- Cystic fibrosis

Lung diseases

- Pulmonary infections
- Lung cancer
- Pulmonary fibrosis

Systemic diseases

- Scleroderma
- Diabetes
- Renal failure

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Asthma: Quintessential Airway Disease

Characterized by:

- Reversible airway narrowing;
- Bronchial hyperresponsiveness;
- Chronic airway inflammation

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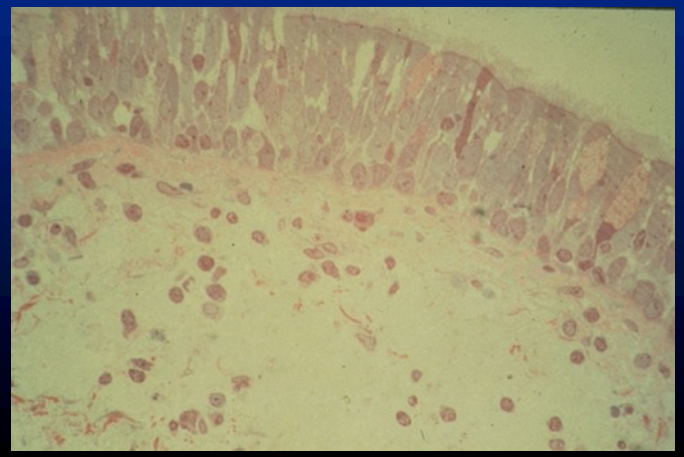
Normal bronchus



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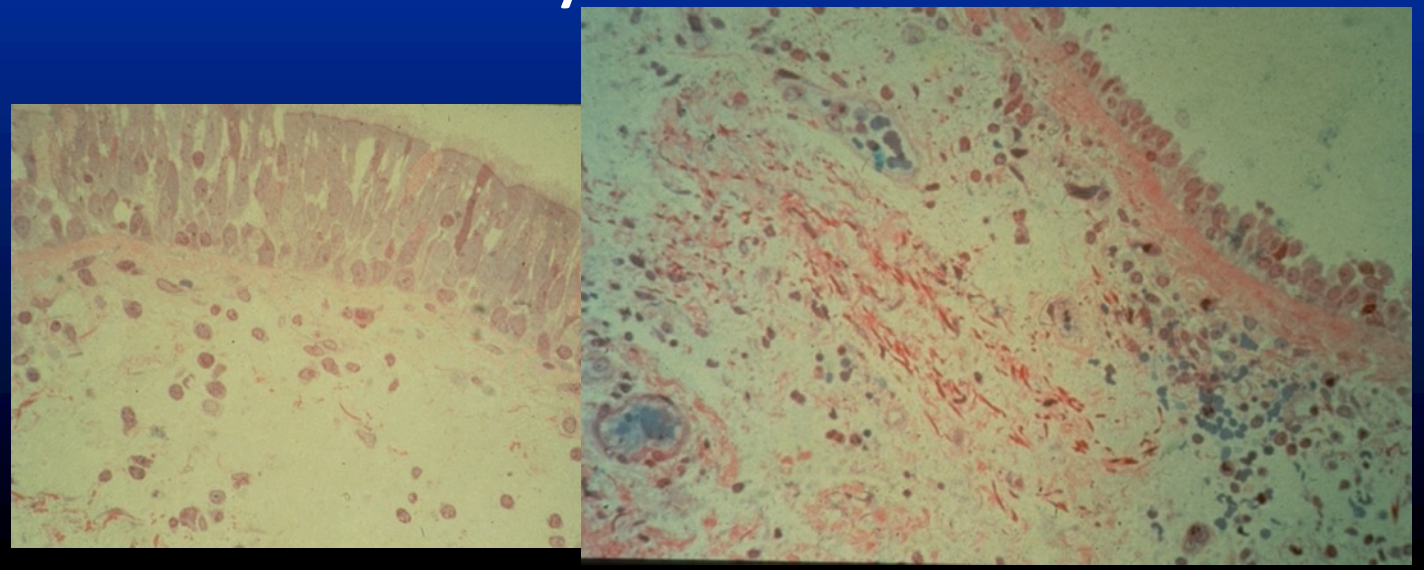

Asthmatic bronchus

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Asthma Syndrome Is Heterogeneous

Asthma **Phenotypes:**

- Age of onset
- Allergic sensitivities
- Severity of regular symptoms
- Susceptibility to exacerbations
- Response to medications

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Asthma Syndrome Is Heterogeneous

Asthma **Endotypes:**

- Eosinophilic (Type-2) inflammation
- Neutrophilic inflammation
- Pauci-granulocytic inflammation

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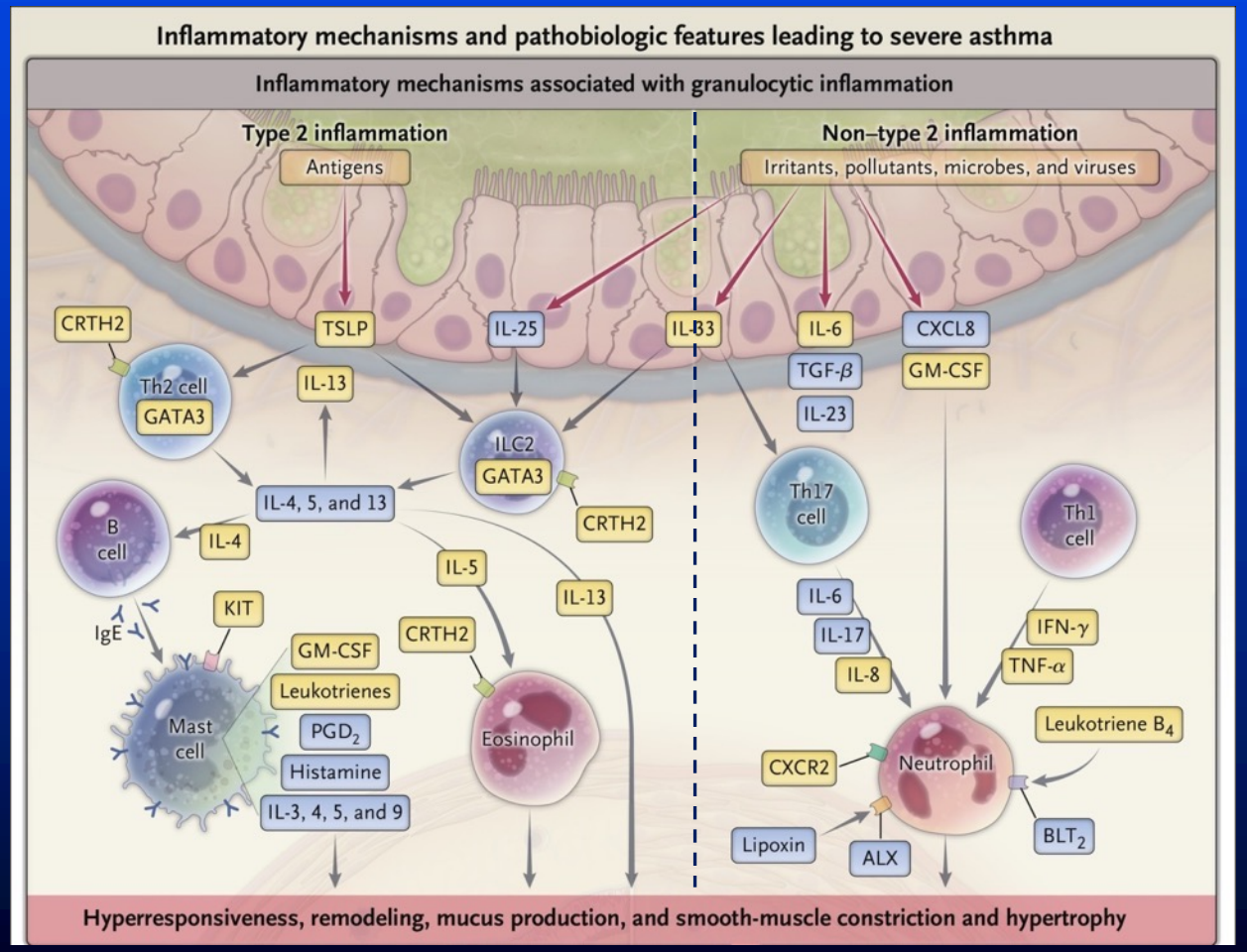
Biochemical Pathways in Severe Asthma



Israel E, et al. *NEJM* 2017: 377:965-76.

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Traditional Disease Markers for Diagnosis and Monitoring Asthma

- Measurement of expiratory airflow
  - Forced expiratory volume in 1 second (FEV1) or peak expiratory flow (PEF)
- Measurement of airway hyperresponsiveness
  - Bronchoprovocative challenge (e.g., methacholine, exercise, hyperventilation of cold air)

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Traditional Disease Markers of Inflammation in Asthma

Markers of inflammation:

- Blood tests for allergy-related proteins (immunoglobulin E) and allergy-related cells (eosinophils)
- Bronchoscopic lavage/airway biopsy
- Sputum analysis (eosinophils)

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Production of Nitric Oxide (NO)

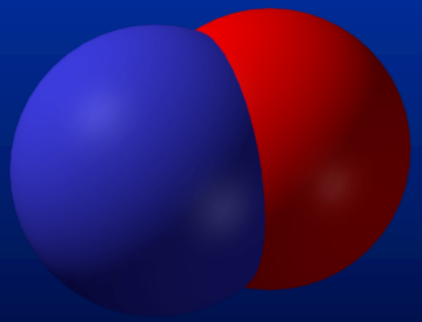
L-Arginine

+

O2

↓

Nitric Oxide



Nitric oxide synthases

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Sources of Inducible Nitric Oxide Synthase (iNOS)

- Airway epithelial cells
  - Increased in airway inflammation
- Especially, eosinophilic airway inflammation

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Sources of Inducible Nitric Oxide Synthase (iNOS)

- Airway epithelial cells
  - Increased in airway inflammation
- Eosinophils

Exhaled NO as a surrogate biomarker for airway eosinophilia/Th2 inflammation

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Measurement of Fractional Concentration of Exhaled NO

+

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Measurement of Fractional Concentration of Exhaled NO

+

NiOx

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Measurement of Fractional Concentration of Exhaled NO

+

→

NiOx

NiOx Mino

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Measurement of Fractional Concentration of Exhaled NO

+

NiOx

NiOx Mino

NiOx Vero

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Measurement of Fractional Concentration of Exhaled NO

- 10-second exhalation at steady pressure to maintain flow rate 50±5 ml/sec.
- Last 3 seconds of exhalation are analyzed by calibrated electrochemical sensor.

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Measurement of Fractional Concentration of Exhaled NO

Ox mino use

(1:55-2:44)

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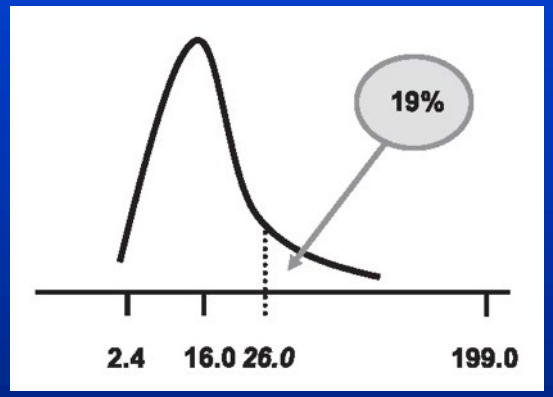
Cut-Off Values for FE_{NO}



Dweik RA, et al. An Official ATS *Clinical Practice Guideline*. *AJRCCM* 2011; 184:602-15.

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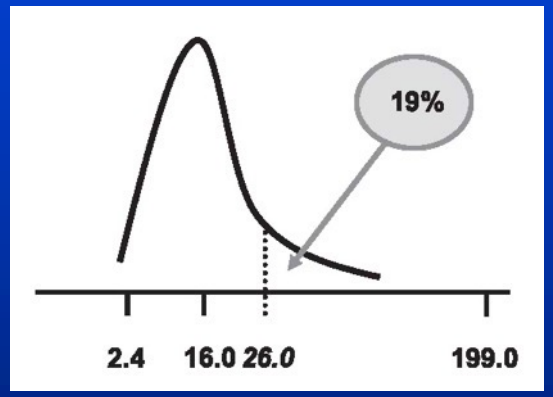

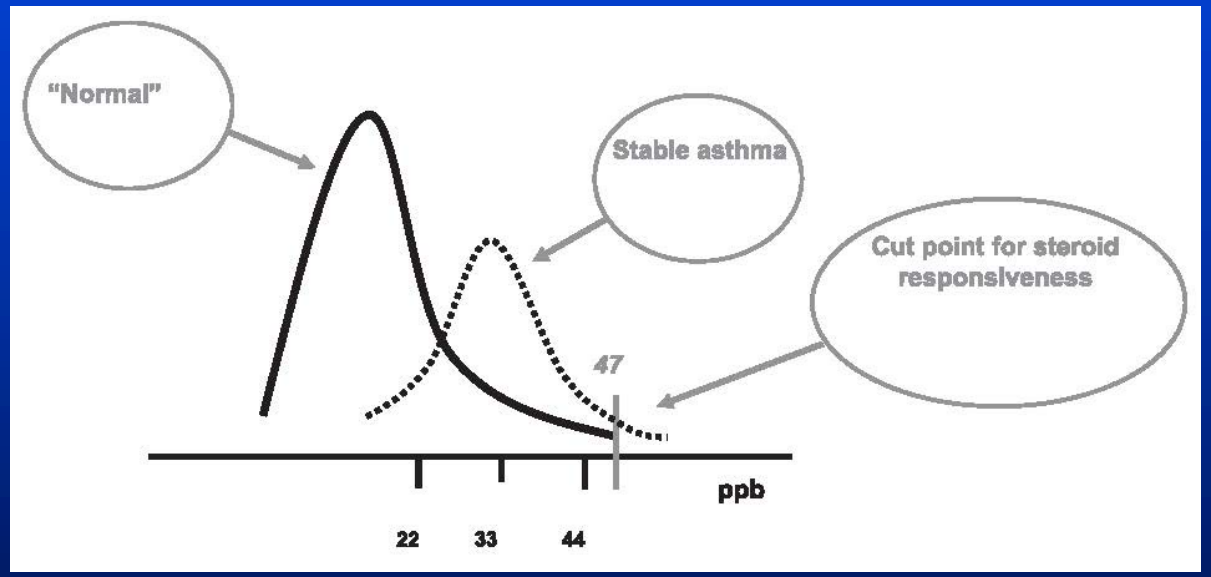

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Cut-Off Values for FE_{NO}

Normal: <25 ppb (<20 in children)

Indeterminate: 25 – 50 ppb (20-35 in children)

High: >50 ppb (>35 in children)

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Modifiers:
Atopy (↑)
Cigarette smoking (↓)
Corticosteroid therapy (↓)
Other: FVC maneuvers; alcohol consumption; nitrate-rich food intake; mouthwash

Significant change in FE_{NO}:
≥20% when FENO >50 ppb
10 ppb when FENO <50 ppb

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American Thoracic Society Statement

"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."

Dweik RA, et al. An Official ATS *Clinical Practice Guideline*. *AJRCCM* 2011; 184:602-15.

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Potential Utility of Measurement of FE_{NO}

1. Diagnosis of asthma
2. Detect eosinophilic inflammation of airways
3. Predict steroid responsiveness in asthma
4. Useful for monitoring asthma activity
5. Assess potential medication non-adherence
6. Characterize asthma endotype in severe asthma

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Correlation with Sputum Eosinophilia (>3%)

- Retrospective analysis
- 295 patients seen at asthma clinic (Liege, Belgium)
- All had confirmed asthma and both measurement of FE_{NO} and sputum induction.

Schleich FN, et al. *Thorax* 2010; 65:1039-44.

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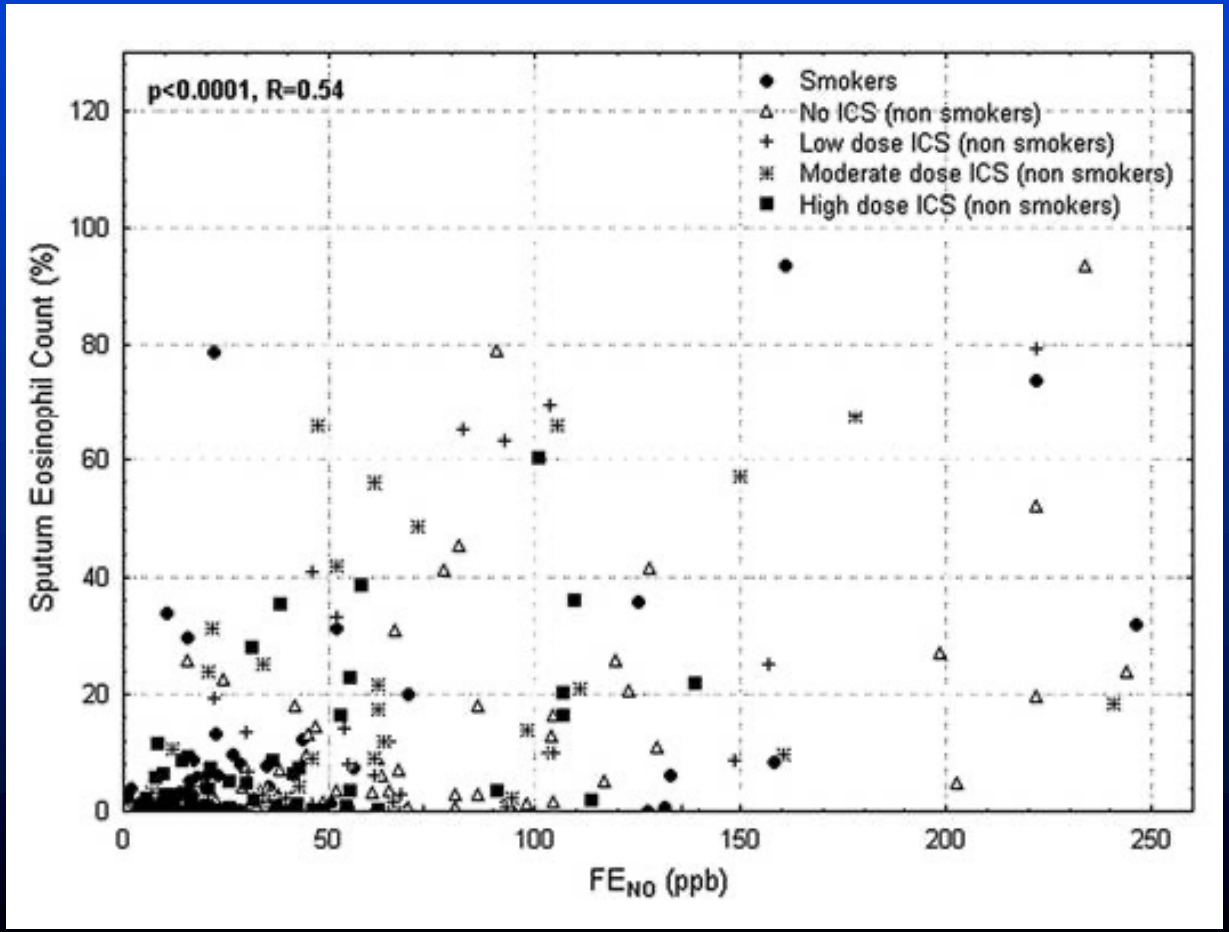

Schleich FN, et al. *Thorax* 2010; 65:1039-44.

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Correlation with Sputum Eosinophilia

A threshold for FE_{NO} of 42 ppb discriminates between eosinophilic and non-eosinophilic asthma with sensitivity of 63% and specificity 80%.

($p<0.0001$ for logistic regression analysis)

Schleich FN, et al. *Thorax* 2010; 65:1039-44.

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Validation of ATS Cut-Off Values: Correlating Sputum Eos

Prospective study of 110 asthma patients at university-based asthma center in Copenhagen.

High FE_{NO} (>50 ppb)	Low FE_{NO} (<25 ppb)
PPV = 77%	**NPV = 88%**

Jeppegaard M, et al. *Respir Med* 2018; 144:22-9.

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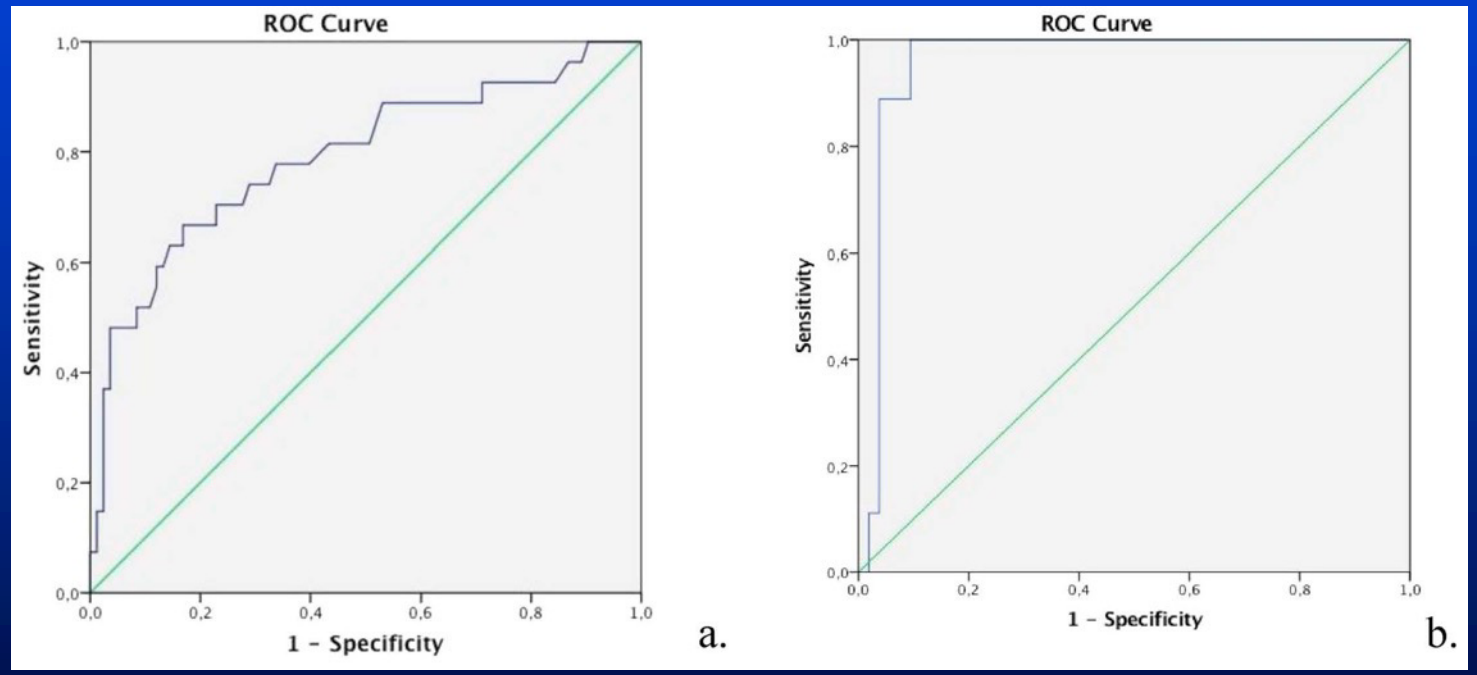
Receiver Operating Characteristic Curves



Total group AUC=0.798

Steroid naive group AUC=0.958

Jeppegaard M, et al. *Respir Med* 2018; 144:22-9.

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Limitations of FE_{NO}

- Considerable overlap between normal and disease
- Influence of modifying factors (age, atopy, sinus disease, cigarette smoking, etc.)
- Dramatic suppression by inhaled corticosteroids
- Values often in a “gray zone” (20-40 ppb)

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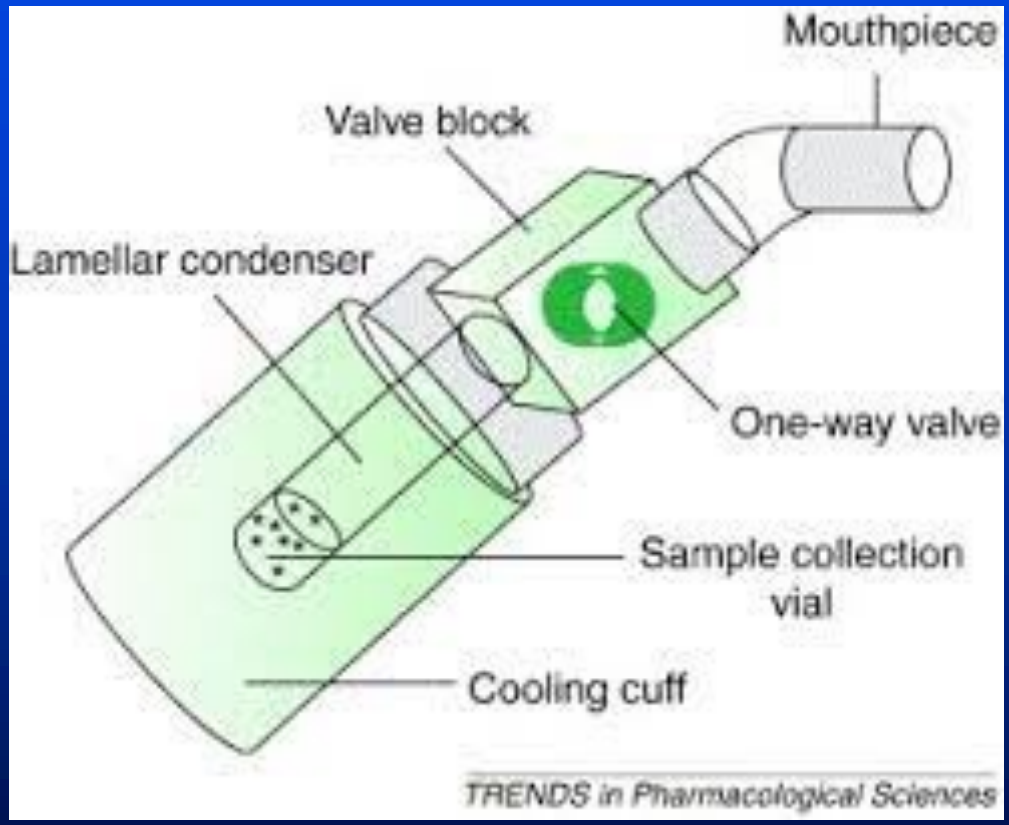
Exhaled Breath Condensate



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Exhaled Breath Condensate

- Volatile and non-volatile compounds
  - Polypeptides
  - Proteins
  - Nucleic acids
  - Lipid mediators
  - Inorganic/organic molecules
  - Redox-relevant molecules
  - pH relevant molecules
  - Cytokines, chemokines

Davis, MD, et al. *Immmunol Allergy Clin North Am* 2012; 32:363-75.

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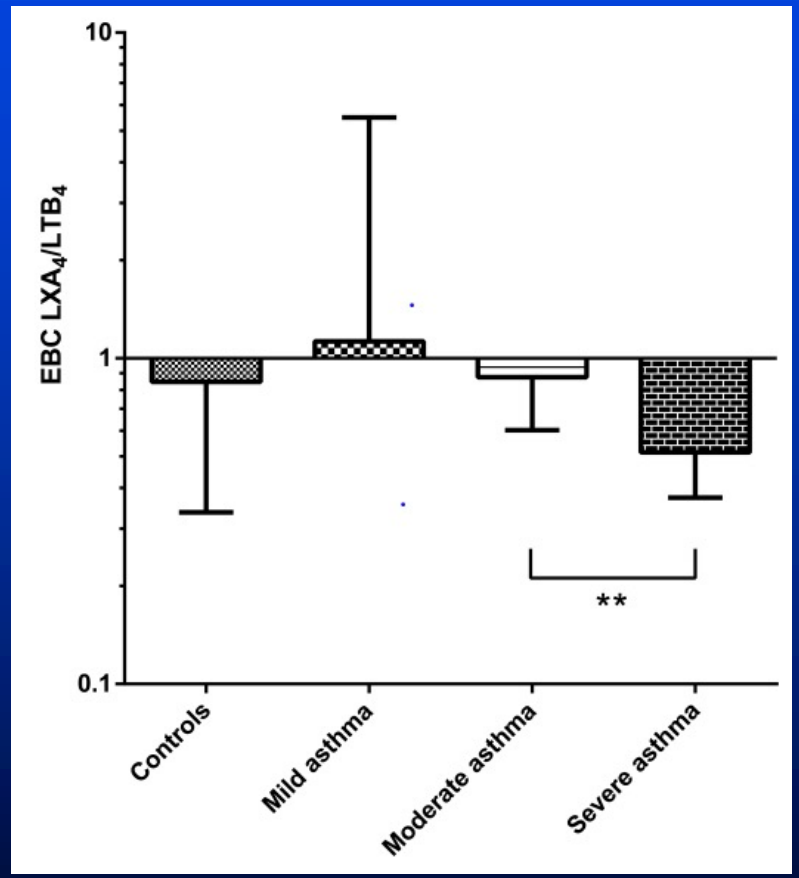
Lipid Mediators in Asthma by EBC

- ↑ pro-inflammatory leukotrienes
- ↑ pro-resolving lipoxins
- ↓ ratio of lipoxins:leukotrienes in severe asthma



Kazani S, et al. *J Allergy Clin Immunol* 2013; 132:547-753.

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VOCs Using Electronic Nose ("Breathomics")

- Diagnostic utility in cancer, infection (including fungal and TB), and airway diseases
- Sensor array vs. targeted molecules via gas chromatography:mass spectrometry

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VOCs in Asthma

245 asthmatic subjects:

Able to discriminate eosinophilic, neutrophilic, and pauci-granulocytic asthma

Eosinophilic:	**Neutrophilic:**
Hexane	Nonanal
2-hexanone	1-propanol
	Hexane

Schleich FN, et al. *Am J Respir Crit Care Med* 2019; 200:444-53.

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Detection of Covid-19 Infection

NASA's E-Nose Device Advanced to "Sniff" COVID-19 from Human Breath

NASA Ames Research Center, April 7, 2021

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Conclusions

- Analysis of components of exhaled breath offers a non-invasive assessment of airway and lung pathology.
- Measurement of exhaled nitric oxide concentration has proven to be a useful marker of eosinophilic airway inflammation in asthma and has been successfully commercialized.
- The science of exhaled breath analysis is in its infancy and has potential for understanding the inflammatory response to inhaled particles.

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