Exhaled Nitric Oxide Testing: When Is It Medically Necessary?

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Overview

- The role of inflammation in asthma
- Asthma biomarkers
- Clinical applications of eNO testing
- Devices approved by the U.S. FDA
- American Thoracic Society clinical practice guidelines
- Health plan coverage
Asthma Snapshot

- Annual asthma costs in the US: >$55 billion
- Among the most common of chronic diseases, but many challenges remain in its diagnosis and management
- The development of asthma is based on complex interactions between host factors, particularly genetic, and environmental exposures (e.g., airborne allergens, viral respiratory infections)
- Inflammation is well established as the primary target for treatment, but variable patterns of inflammation suggest phenotypic distinctions that can impact disease presentation and treatment response

CDC. Asthma in the US. Available at: http://www.cdc.gov/vitalsigns/asthma/.
The Role of Inflammation in Asthma

- Chronic inflammatory disorder of the airways
  - May cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
  - Widespread but variable airflow obstruction resolves spontaneously or with treatment
  - Inflammation may cause an increase in existing bronchial hyperresponsiveness to a variety of stimuli

- Cells and cellular elements that play a role:
  - Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells
Measuring Inflammation in Asthma

- Currently no direct measure is widely available clinically
- Treatment decisions are based on indirect measures
  - Spirometry measures
    - Used most frequently to assess risk of future adverse events
    - Forced expiratory volume in 1 second (FEV₁), reported as a percent of the predicted value or as a proportion of the forced vital capacity (FEV₁/FVC)
  - Symptom scores
  - Rescue medication use
  - Other indicators of disease activity
Potential Asthma Biomarkers

- Airway hyperresponsiveness
- Blood or sputum eosinophils
- Eosinophilic cationic protein
- Serum immunoglobulin E
- Fractional eNO concentration
- Various metabolites in exhaled breath condensate
Nitric Oxide Affects Many Organ Systems

- Acts as a bronchodilator in the lungs
- Produced by various lung cells from the amino acid L-arginine by different isoenzymes of nitric oxide synthase
Analysis of eNO

• Proposed as a marker of inflammation
• Could be useful in:
  - Diagnosing and monitoring disease activity
  - Directing treatment in patients with asthma and other pulmonary conditions
• Levels of eNO have been shown to be:
  - Elevated in patients with asthma
  - Higher during periods of acute exacerbation
  - Correlated with other measures of inflammation
Clinical Applications of eNO Testing
The Role of eNO in Asthma Diagnosis

- Measurement of eNO can differentiate chronic cough due to asthma versus other causes
- Individuals with chronic cough due to asthma have significantly elevated eNO levels compared with those with nonasthmatic cough
- Studies have shown that eNO is:
  - Equivalent to standard outcomes as a discriminator between patients with and without asthma
  - At least comparable to other traditional methods for asthma diagnosis

Parameswaran et al. *Can Respir J.* 2001;8:239-244.
Asthma Management: eNO Predicts Response to Therapy

- Used to predict response to therapy in patients with asthma treated with corticosteroids
- Levels of eNO, which is one of the earliest responding markers, decrease after corticosteroid therapy for asthma

Asthma Management: Using eNO to Assess and Improve Asthma Control

- Decreased eNO levels reflect a decrease in asthmatic inflammation, indicating response to therapy
- eNO measurement may be used as a basis for:
  - Treatment change (evidence suggests a correlation between eNO levels and reactivity and eosinophilic inflammation)
  - Monitoring adherence to therapy (levels of eNO have been shown to rise rapidly after steroid withdrawal)

Other Respiratory Diseases Associated With Altered eNO Levels

- Bronchochiectasis, cystic fibrosis, and sarcoidosis
- Chronic obstructive pulmonary disease (COPD)
- Nonasthmatic eosinophilic bronchitis
- Upper respiratory infections

Devices Approved by the FDA

• NIOX Breath Nitric Oxide Test System
  - Approved in 2003 for evaluating an asthma patient’s response to anti-inflammatory therapy
  - Measures changes in fractional eNO concentration as an adjunct to established clinical and laboratory assessments of asthma

• NIOX MINO
  - Approved in 2008 to measure fractional eNO in human breath

• Apieron INSIGHT eNO System
  - Approved in 2008 to quantitatively measure eNO in expired breath as a marker of inflammation for patients with asthma
ATS Clinical Practice Guideline
Recommendations

• The use of eNO in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence)

• The use of 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)

• eNO may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence)

• The use of eNO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence)

ATS Clinical Practice Guideline Recommendations (cont’d)

- Given the long-established relationship between eosinophilic inflammation and steroid responsiveness in airway disease, the finding that eNO correlates with eosinophilic inflammation suggests its use as an indirect indicator of eosinophilic inflammation and the potential for steroid responsiveness.
- Because not all patients respond to corticosteroids, eNO may be used to help decide who might benefit from steroid treatment and who should try other medications, and to determine whether steroid therapy may be safely withdrawn.
- Increased eNO provides supportive, rather than conclusive, evidence for an asthma diagnosis.

ATS Clinical Practice Guideline: Cut Points for Analyzing eNO Results

- Low eNO (<25 ppb in adults and <20 ppb in children) implies noneosinophilic airway inflammation or the absence of airway inflammation.
- A high eNO (>50 ppb in adults and >35 ppb in children) or a rising eNO with >40% change from a previously stable level implies uncontrolled or deteriorating eosinophilic airway inflammation.
- Values of eNO between 25 and 50 ppb in adults (20 to 35 ppb in children) should be interpreted cautiously with reference to the clinical situation.

Health Plan Coverage

- Most health plans do not cover measuring eNO levels for any indication
- Due to limited data, the test is still considered experimental and investigational
Sample Plan Language

- Measurement of exhaled nitric oxide in the diagnosis and management of respiratory disorders is considered experimental or investigational based upon insufficient scientific evidence to permit conclusions concerning the effect on health outcomes. These respiratory disorders include, but are not limited to: asthma, chronic obstructive pulmonary disease, and chronic cough.
- The measurement of exhaled nitric oxide is not covered for any indication, including the management of asthma and/or other respiratory disorders, because it is considered experimental, investigational, or unproven.
The Role of External Independent Medical Review in Determining Medical Necessity

- Allows access to a range of board-certified physician specialists who keep up-to-date with the latest medical research literature and with the latest standard of care
- Provides specialty match to allow healthcare plans to ensure that the requested procedure/treatment falls under the medical necessity requirements
  - Reviewers stay on top of procedures/treatments as they are studied more extensively and potentially accepted into clinical guidelines
- Avoids conflicts of interest, which can relate to economics, lack of specialists to review cases, or having the same doctor who denied a case review an appeal
Conclusions

- Measurement of eNO has been proposed as a marker of inflammation that could be useful in diagnosing and monitoring disease activity and directing treatment in patients with asthma.
- Although nitric oxide levels may be accurately measured, there is currently limited evidence in the published medical literature for most health plans to cover testing.
- Ongoing and future studies may lead to widespread acceptance of the procedure, which provides patient-specific information that may facilitate individualization of treatment for patients with asthma.
Questions & Answers
Thank you for attending. All participants will receive a free copy of our latest publication via email:

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