Clinical Allergy Tips
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From the Editor: The fractional exhaled NO concentration (FENO) is presently considered to be a useful instrument for the diagnosis and follow up of asthmatic patients. In this Clinical Allergy Tip, Dr. Krzysztof Kowal provides practical information on how to use this tool in clinical practice.

Evaluation of Exhaled Nitric Oxide in Clinical Practice
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Nitric oxide (NO) is a gaseous molecule produced during L-arginine metabolism in a reaction catalyzed by the nitric oxide synthase (NOS). Nitric oxide is present in the exhaled air at very low concentrations which are expressed as FENO (the fractional exhaled NO concentration) in parts per billion (ppb) units. Currently available chemiluminescence analyzers enable evaluation of FENO “on line”, which makes the test suitable for clinical practice.

The expression of NOS in the airways is up-regulated by inflammatory cytokines particularly interleukin (IL)-4 and IL-13. Therefore, frequently FENO is considered to be a surrogate marker of airway eosinophilic inflammation, however, therapies targeting directly eosinophils, such as mepolizumab decrease eosinophilia with no effect of FENO.

Main clinical application of FENO measurement:
1. Asthma diagnosis
2. Asthma monitoring
3. Selection of patients sensitive to inhaled corticosteroid (ICS) therapy

Majority of asthmatic patients are characterized by Th2-type airway inflammation. Demonstration of elevated FENO may help to diagnose some asthma phenotypes.
Table 1 Interpretation of $\text{FE}_{\text{NO}}$ values in patients not receiving ICS.

<table>
<thead>
<tr>
<th>Adults</th>
<th>$\text{FE}_{\text{NO}} &lt; 25 \text{ ppb}$</th>
<th>$25 \text{ ppb} \leq \text{FE}_{\text{NO}} \leq 50 \text{ ppb}$</th>
<th>$\text{FE}_{\text{NO}} &gt; 50 \text{ ppb}$</th>
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<tbody>
<tr>
<td>Children &lt;12 years of age</td>
<td>$\text{FE}_{\text{NO}} &lt; 20 \text{ ppb}$</td>
<td>$20 \text{ ppb} \leq \text{FE}_{\text{NO}} \leq 35 \text{ ppb}$</td>
<td>$\text{FE}_{\text{NO}} &gt; 35 \text{ ppb}$</td>
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<tr>
<td>Interpretation</td>
<td>Th2-type inflammation unlikely</td>
<td>Depends on the clinical status</td>
<td>Th2-type inflammation highly likely</td>
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<tr>
<td></td>
<td>Clinical response to ICS unlikely</td>
<td></td>
<td>Clinical response to ICS highly likely</td>
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</tbody>
</table>

In asthmatic patients increase and decrease of $\text{FE}_{\text{NO}}$ reflects exacerbation and remission of airway inflammation respectively. Significant increase in Th2-type airway inflammation usually is associated with greater than 20% and 25 ppb increase of $\text{FE}_{\text{NO}}$.

Significant decrease of $\text{FE}_{\text{NO}}$ is considered when the level decreases by at least 20% in patients with original values greater than 50 ppb or at least 10% in those with original values less than 50 ppb.

Clinically, increase of $\text{FE}_{\text{NO}}$ may reflect uncontrolled asthma and predict asthma exacerbations.

**Factors associated with increase of $\text{FE}_{\text{NO}}$:**
1. Exposure to factors which augment airway inflammation such as
   a. allergens or infections
2. Older age
3. Atopy
4. Drugs
   a. L-arginine
   b. Enalapril
   c. Sodium nitroprusside
5. Food contamination
   a. Arginine or nitrite

**Factors associated with decrease of $\text{FE}_{\text{NO}}$:**
1. Smoking
2. Ingestion of
   a. Caffeine
   b. Alcohol
3. Hyperventilation due to
   a. Exercise
   b. Spirometry
4. Bronchiectasis
5. Drugs
   a. Corticosteroids
6. Allergen immunotherapy

The $\text{FE}_{\text{NO}}$ is flow-dependent, therefore the measurements should be performed at constant exhalation rate (50 ml/sec is recommended).

In clinical practice evaluation of $\text{FE}_{\text{NO}}$ is particularly useful when demonstration of Th2-type airway inflammation is helpful in decision making concerning diagnosis or therapy.

In patients with nonspecific respiratory symptoms such as those with chronic cough, evaluation of $\text{FE}_{\text{NO}}$ is helpful in establishing asthma diagnosis with high positive and negative predictive values.

In patients treated with inhaled corticosteroids and long acting beta agonists in whom increasing airway inflammation could not be perceived by a patient or documented by traditional methods such as spirometry evaluation of $\text{FE}_{\text{NO}}$ may help in adjustment of corticosteroid dose.
When tailoring inhaled corticosteroid dose the effect on $\text{FE}_{\text{NO}}$ can be seen earlier, usually within several days, than their effect on asthma control or asthma exacerbation rates.

In asthmatic patients with severe obstruction interpretation of $\text{FE}_{\text{NO}}$ should be made cautiously.

Finally, evaluation of $\text{FE}_{\text{NO}}$ is useful to assess Adherence to ICS therapy.