The Role of FeNO in Asthma Management

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Fractional Exhaled Nitric Oxide

- FeNO
  - *"a measure of eosinophilic airway inflammation that is convenient and easy to use"*
  - Does it add anything??

Photo from the Nobel Foundation archive.

Robert F. Furchgott

Prize share: 1/3

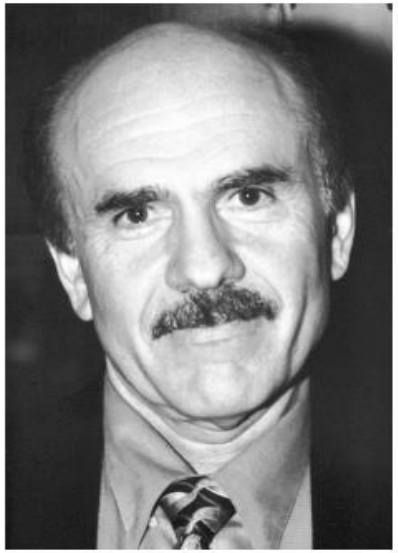

Photo from the Nobel Foundation archive.

Louis J. Ignarro

Prize share: 1/3

Photo from the Nobel Foundation archive.

Ferid Murad

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1998 was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system"

Nitric Oxide – what is it??

- Produced in the airways
  - multiple physiologic roles – eg regulator of airway inflammation, lung development, smooth muscle relaxation, ciliary motility
- A product of inflammation/infection in the airway that is overproduced in asthma
  - In allergic and eosinophilic asthma, epithelial exposure to IL-13 induces nitric oxide synthase (iNOS) to increase production of nitric oxide
- Nitric oxide can be measured by FeNO

Comparison with the 'gold standard'

- Sputum eosinophils is considered the 'gold standard' measure of T2 airway inflammation
  - Requires considerable laboratory support
- FeNO accurately predicts sputum eosinophilia
  - Not always perfectly accurate…does this make FeNO an inferior test?
- FeNO and sputum eosinophilia result from different inflammatory pathways
  - IL-4 and IL-13 increase FeNO levels
  - IL-5 involved in development/recruitment/activation of eosinophils
  - *'FeNO isn't a surrogate marker of sputum eosinophils, but a parallel marker of airway inflammation that is often, but not always associated with eosinophilia'*
  - → so measuring both FeNO and blood eosinophils provides more info than measuring either alone

When is FeNO useful??

- Workup for possible asthma…
- Established asthma, poorly controlled…
- Established asthma, minimal or no symptoms…
- Severe asthma, on maximal inhaler therapy…
- Acute asthma…

Workup for Possible Asthma

- *Does FeNO have a role in the diagnosis of asthma?*

- Definition of asthma:
  - Typical symptoms (breathlessness, cough, wheeze) PLUS objective evidence of excessive airway calibre fluctuation, eg
    - Peak flow variability
    - Bronchodilator reversibility
    - Airway hyper-responsiveness (broncho-provocation)
    - Improvement in FEV1 (12% & 200ml) after a course of corticosteroid treatment
  - *What does FeNO add?*

What does FeNO add to the diagnosis of asthma?

Patients suspected to have asthma, in whom the diagnosis is <u>not</u> established on initial spirometry testing

- FeNO >50ppb has 90% specificity, and is supportive of a diagnosis of asthma
  - Pitfalls:
    - Also elevated in eosinophilic bronchitis, CRSwNP, atopy
- FeNO <40ppb doesn't rule out asthma
  - Can be reduced by treatment (ICS), smoking, reduced airway calibre (false negative)
  - Not all asthma is defined by eosinophilic inflammation

Patients suspected to have asthma, in whom the diagnosis <u>is</u> established on initial spirometry testing

- Prognostic information
  - Greater risk of symptoms, lung function decline, exacerbations
- A predictor of treatment response
  - FeNO >50ppb strongly indicates the patient will be responsive to ICS therapy

Use of FeNO in established, poorly controlled asthma

Is the asthma poorly controlled due to persistent eosinophilic airway inflammation????

- *FeNO elevated → Yes*
  - Revisit ICS therapy – check compliance, appropriateness of device, inhaler technique
  - Escalate ICS therapy
  - Consider advanced therapy
- FeNO not elevated → probably not
  - Consider other reasons for poor control
    - Asthma due to other inflammatory pathways (infection/neutrophilic)
    - Mechanical factors/fixed airflow obstruction
    - Extra-thoracic factors (obesity/deconditioning etc)
    - Contributing comorbidities eg COPD/sino-nasal disease/bronchiectasis/heart disease

Use of FeNO in established, well-controlled asthma

- Elevated FeNO with minimal symptoms still provides very valuable prognostic information

- Patients with elevated FeNO (eg >35)
  - Greater airflow obstruction
  - Greater airway reactivity
  - Decline in lung function over time
  - More ED visits and ICU admissions
  - **Higher overall risk of exacerbations**

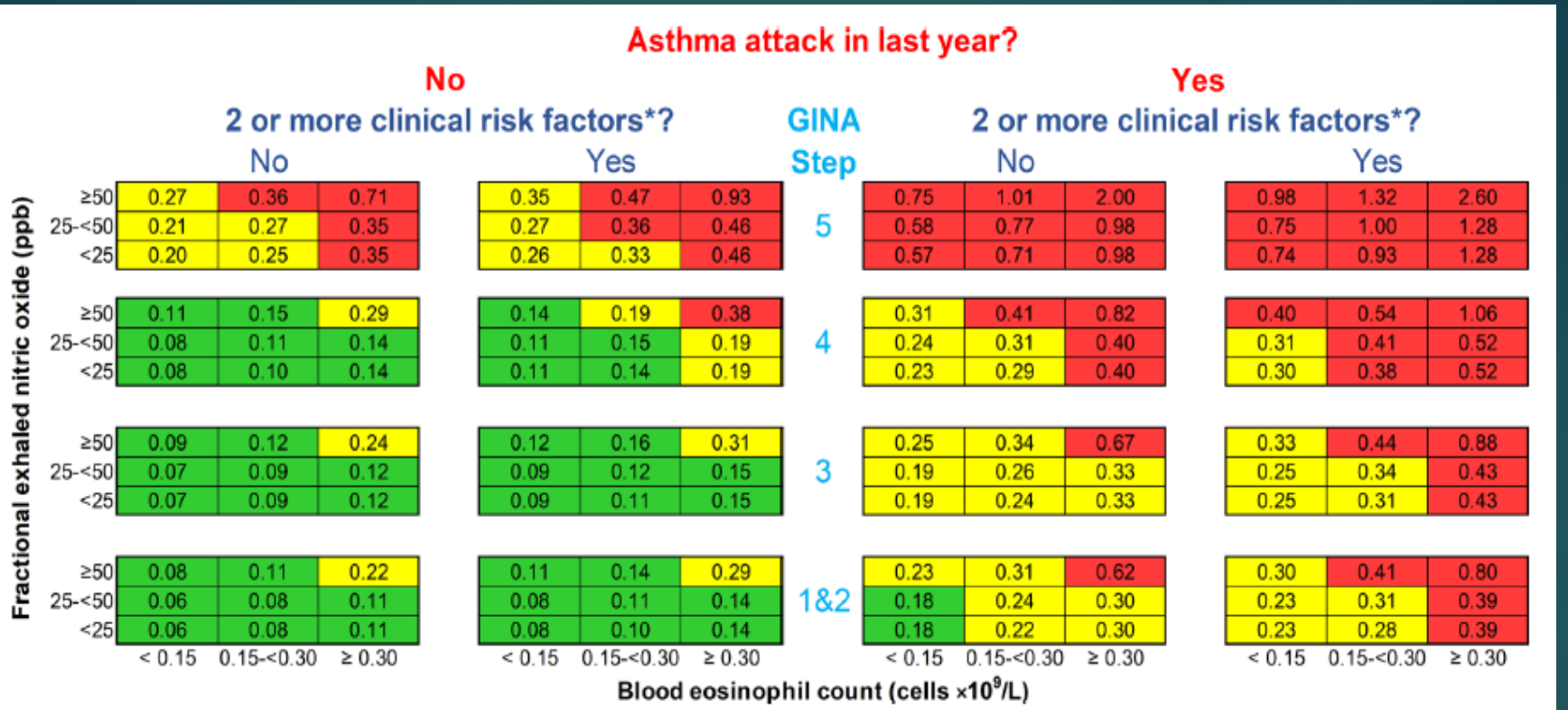

Figure 1 Prototype asthma attack risk scale. Numbers in each cell are predicted annual asthma attack rates for patients over the age of 12 if treatment is not changed. An asthma attack is an episode of acute asthma requiring treatment with systemic steroids ≥3 days and/or hospitalisation. The blood eosinophil count is contemporaneous or the highest result in the last 12 months; fractional exhaled nitric oxide level is contemporaneous. *Risk factors are defined by the Global Initiative for Asthma (GINA) guidelines[1]: poor symptom control (Asthma Control Questionnaire score ≥1.5), low lung function (forced expiratory volume in 1 second <80% predicted), adherence issues, reliever overuse (>200 dose of salbutamol cannister/month), intubation or intensive care unit admission for asthma previously, comorbidities (one of chronic rhinosinusitis, obesity and psychiatric disease) and environmental exposures (one of smoking, allergen and pollution).

Couillard S, Laugerud A, Jabeen M, et al. Thorax 2022;**77**:199–202.

Use of FeNO in severe asthma

- Persistent poorly controlled asthma and ongoing eosinophilic inflammation despite optimal high dose inhaler therapy → consider biologic therapy →
  - 4 options:
    - Omalizumab (anti-IgE)
    - Mepolizumab (anti-IL5)
    - Benralizumab (anti-IL5R)
    - Dupilumab (anti-IL4/IL13)
  - FeNO can assist this decision!

FeNO and Biologic therapy

Use of FeNO to predict response to biologic therapy

- FeNO >19.5 predicts response to Omalizumab
- FeNO >25 predicts response to Dupilumab
- Mepo and Benra are effective, independent of baseline FeNO levels

Use to evaluate response to Dupilumab

- Dupilumab should reduce FeNO.
  - If ongoing uncontrolled asthma on Dupilumab, with suppressed FeNO – consider other cause of poor asthma control

FeNO in Acute Asthma

- FeNO is often elevated in acute asthma
  - Mostly cross-sectional studies, not incorporating baseline data
    - Eg is FeNO elevated
      - because of the acute exacerbation,
      - or because of the underlying asthma
- Also applies to severe asthma, on biologic therapy
  - Exacerbations can be eosinophilic or non-eosinophilic, and FeNO can discriminate
- *Should non-eosinophilic exacerbations be receiving oral steroids??*

Summary

- FeNO…
  - is a measure of eosinophilic airway inflammation that is convenient and easy to use
  - Adds diagnostic information
    - High FeNO predicts asthma
    - Low FeNO suggests an alternate diagnosis should be sought
  - Adds prognostic information
    - High FeNO predicts future risk of exacerbation, lung function decline
  - Guides therapy
    - High FeNO predicts good response to ICS
    - Assists biologic therapy choice