Factors that affect FeNO in Asthma

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Objectives

- Review the FeNO values and factors in children and adults
- Discuss the effect of atopy on FeNO in asthmatics
- Discuss the pitfalls in study designs and shortcomings of FeNO
- Discuss the use of FeNO to identify specific phenotypes and their management

Factors Affecting FeNO Levels

- Airway infection
- Atopy (high levels)
- Age / Height / Sex
- Race / Ethnicity
- Time of day (AM)
- Anti-inflammatory therapy
- Smoking
- Exercise / Spirometry
- Cystic fibrosis
- Ciliary dyskinesia
- Pulmonary hypertension

Normal FeNO levels at 50 mL/s

- Adult controls: Mean 16 ppb in men and 12.6 ppb in women
- Adult asthma: Upper limit is 29 ppb in men and 21.5 ppb in women
- Pediatric controls: Mean 8 ppb at age 6-11 and 11 ppb for adolescents
- Pediatric asthma: Upper limit is 15 ppb at age 4 and 26 ppb for adolescents

Reference Values for FeNO

FeNO in Asthma and Atopy

- 12,408 random subjects aged 6-80 years from NHANES
  - Both FeNO and eosinophils at intermediate & high levels were independently associated with asthma, wheeze, and asthma attacks
  - Intermediate & high eosinophils were associated with asthma related ED visits
  - Both airway and systemic mechanisms trigger clinical asthma and their assessments have specific markets
- 250 children aged 11-13 years at risk for allergy/asthma
  - 97 children had FeNO, PST, Indoor allergens measured
  - Increased FeNO levels were highest in both mite-sensitized and mite-exposed
  - The active allergen exposure effect is greater in elevating FeNO than just sensitization
Asthma Prevalence and FeNO in relation to Sensitization

FeNO in Asthma and Atopy

- Increased FeNO was independently associated with having IgE antibodies to food allergens: Peanut, soy, shrimp, egg, milk, fish, wheat
- Even food sensitization must be assessed to fully understand asthma inflammation
- Children with clinical peanut allergy had increased FeNO compared to those with peanut tolerance. Ara H2 specific-IgE and FeNO each showed improved diagnostic accuracy compared to skin prick test.
- Adding FeNO to Ara H2-IgE would reduce risk of an unsuccessful food challenge to peanut.

FeNO in Adult Asthma Phenotypes

- 446 adults enrolled in SARP divided into Severe (SA) and Nonsevere (NA) asthma and controls, based on ATS refractory asthma criteria
- SA (n=175, %FEV1 58±20), NA (n=271, %FEV1 83±16)
- High FeNO (>35 ppb) levels: No difference between groups (40% in each)
- But high FeNO differentiated more airway reactivity, AW inflammation, atopy, hyperinflation, decreased sx awareness, less MD visits and more ER visits
- High FeNO had lower FEF 25-75, but both groups similar in %FEV1 and ratio
- High FeNO group were younger and diagnosed with asthma younger, male
- NA and high FeNO shared more similarities with SA and high FeNO than NA and low FeNO

FeNO in Pediatric Asthma Phenotypes

- 120 asthmatic children, 6-12 years, 21 sensitization, 4 weeks after exacerbation and/or oral or ICS treatment (Trousseau Asthma Program)
- Clustered into 4 groups based on 18 variables
  1. Multiple Allergies and Severe Asthma (n=20)
  2. Pollen Sensitization with Severe Exacerbations (n=12)
  3. Multiple Allergies, Sensitization and Mild Asthma (n=36)
  4. Dust Mite Sensitization and Mild Asthma (n=56)
- Cluster 1: 95% moderate-severe asthma severity, 100% multiple sensitizations, 90% eczema, lowest FEF 25-75, highest IgE, FeNO 87 ppb
- Cluster 2: 92% moderate-severe asthma severity, 92% pollen sensitization, lower IgE, FeNO 56 ppb
- Cluster 3: 100% mild asthma severity, 93% multiple sensitizations, normal FEF 25-75, lower IgE, FeNO 55 ppb
- Cluster 4: 74% mild asthma severity, meseo-asthmatic (mostly males), intermediate FEF 25-75, Intermediate IgE, FeNO 46 ppb

Conclusions: Factors affecting FeNO

- Age, height, and time of day should be controlled similar to spirometry.
- Active smoking, upper/lower respiratory infection within 2 weeks, and the use of any anti-inflammatory medication within 4 weeks should be excluded or duly noted.
- Study designs with FeNO to be clinically meaningful should not exclude non-compliance.
- Study designs with FeNO should control baseline or phenotype characteristics of patient’s atopy (serum markers and atopic diseases) due to varying responses.