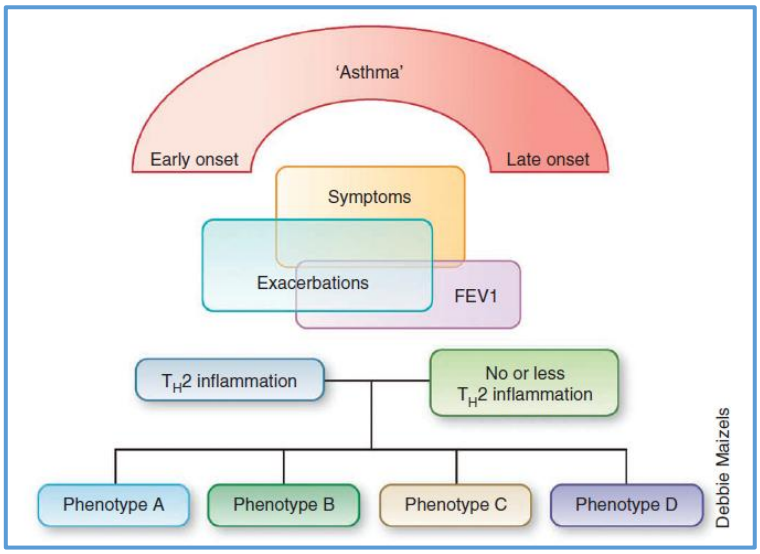
Topic: FeNo as a diagnostic tool in identifying 'TH2 inflammatory asthma' and the potential to act as a marker for corticosteroid responsiveness and marker of well-controlled Asthma treatment.

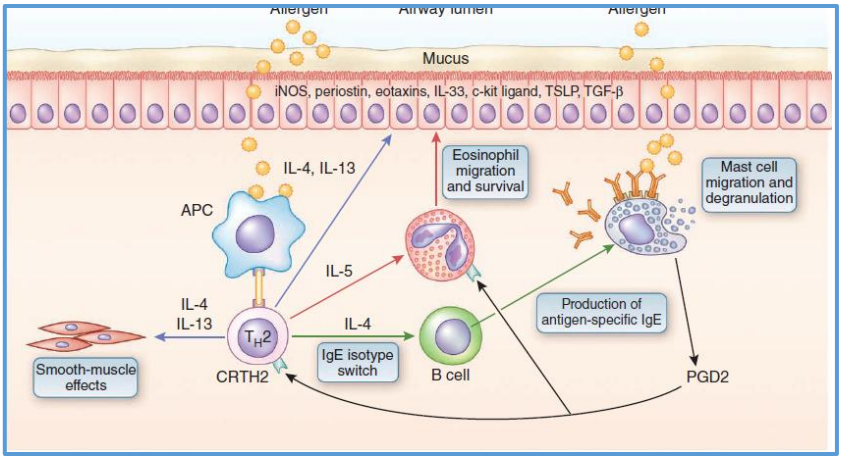
- Introduction to asthma diagnosis
- Introduction to FeNo and how it can be applied as a diagnostic tool
- Discussion on data, guidelines and clinical experience around use of FeNo
- Any opportunities for future research
- Any key takeaways for HCPs to apply for their clinical practices

Asthma affects 5–10% of the population in many developed countries and is associated with a large socioeconomic burden. 'Asthma' is a vague term that describes a group of clinical symptoms with reversible expiratory airflow limitation and/ or bronchial hyper-responsiveness (1). Asthma to most clinicians is a heterogeneous condition characterized by respiratory symptoms (wheeze, cough, breathlessness, chest tightness and pain) associated with variable airflow obstruction, hyper-responsiveness and often an underlying inflammation (2).

There is no single defining feature or symptom of asthma; however, airway variability is essential to making a diagnosis of asthma, therefore diagnosis of asthma is achieved through a holistic evaluation of patient symptoms over a period of time alongside repeated physiologic evaluation of lung function, and assessment of response to treatment. Thus, the term asthma, like 'arthritis', equates to a definition of grouped clinical and physiological characteristics (Fig. 1).



In the 1990s and early 2000s, this vague clinical definition of asthma led to successful clinical trials of nonspecific anti-inflammatory and bronchodilator medications. At the same time, researchers working with mouse models of allergic asthma and/or inflammation identified the crucial role of T helper (TH2) immune pathway elements (Fig. 2) in both inflammation and airway hyper responsiveness of the airway (3-5).



Although, Asthma is a heterogeneous, chronic disease as mentioned above it is characterized by two fundamental and interrelated abnormalities: airway inflammation and airway hyper-responsiveness which can clearly be divided into two broad groups those with TH2 inflammation and those with no TH2 inflammation (6).

In allergic asthma, which is the underlying cause of asthma for up to 80% of children and approximately 50% of adults (7-9) airway inflammation results from the activation of mast cells and antigen-specific TH2 cells, resulting in the production of cytokines, including interleukin (IL)-4, IL-5 and IL-13. In turn, IL-4 and IL-13 cause epithelial inducible nitric oxide synthase (iNOS) expression to be upregulated via signal transducer and activator of transcription (STAT)-6, a process resulting in higher levels of fractional exhaled nitric oxide (FeNO) and is a corticosteroid sensitive process (11).

'Point-of-care' measurement of allergic airway inflammation via assessment of increased fractional exhaled nitric oxide (FeNO) in asthmatics has become available with various commercially available FeNO machines, which be easily used within the primary care setting.

The purpose of this article, therefore, is to help the reader understand whether

1. **Can FeNO be used as a 'point of care test' to identify those asthmatics which compromise 80% of children and approximately 50% of adults, (7-9) whose airway inflammation results from the activation of mast cells and antigen-specific TH2 cells with associated TH2 Inflammation?**
2. **Once FeNO has identified these patients are these also the cohort of patients who are more likely respond to corticosteroid therapy and also therefore could FeNO be used as a test to assess compliance with treatment.**

The FeNO test

FeNO testing is a quantitative, non-invasive, simple and safe test making it suitable for use in the primary care setting with appropriate training of health care professional with responsibility for delivering and interpreting the results (12)

The FeNO test measures the level of FeNO in the exhaled breath. FeNO testing conducted using a handheld device into which the patient blows for 10 seconds at 60 litres a minute. A shorter test is available for children. The result provided within approximately 1 minute with a FeNO level ≥35 ppb as a positive test in children and a level ≥40 ppb as a positive test in adults (13).

The FeNO test does however have both false positives and false negatives and therefore the healthcare professional performing the test needs to be aware of these (10) (Box 3). The performer must also be aware that there is some overlap between FeNO levels among individuals with or without asthma (12). An evaluation of the results of eight studies among adults within the

secondary care setting suggested that around 1 in 5 individuals with a positive FeNO test will not have asthma (false positive) and around 1 in 5 people with a negative FeNO test will have asthma (false negatives) (10).

Box 3: Confounding factors that may result in an increased or decreased FeNO level[1]

Confounding factors that may INCREASE FeNO levels	Confounding factors that may DECREASE FeNO levels
FeNO levels may be higher than population norms in: • Men, tall individuals and those consuming a diet high in nitrates FeNO levels may be elevated in: • Patients with allergic rhinitis exposed to an allergen even in the absence of respiratory symptoms • Patients with active rhinovirus infection	FeNO levels may be lower than population norms in: • Children (a lower reference range must be used) FeNO levels may be reduced in: • Cigarette smokers • Patients recently treated with inhaled or oral corticosteroids

Box 1: NICE guidance for the role of FeNO is the evaluation and diagnosis of asthma in children over 5 and adults[6]

FeNO in the diagnosis of asthma in children

- Consider a FeNO test in children and young people (aged 5-16 years) if there is diagnostic uncertainty after initial assessment and they have either:
  - Normal spirometry or
  - Obstructive spirometry with a negative bronchodilator reversibility test. **Regard a FeNO level of ≥35 ppb as a positive test**
- Suspect asthma in children and young people (aged 5-16 years) if they have **symptoms suggestive of asthma** and:
  - A FeNO level ≥35 ppb with normal spirometry and negative peak flow variability or
  - A FeNO level ≥35 ppb with obstructive spirometry but negative bronchodilator reversibility and no variability in peak flow or
  - Normal spirometry, a FeNO level ≤34 ppb and a positive peak flow variability
- Diagnose asthma in children and young people (aged 5-16 years) if they have **symptoms suggestive of asthma** and:
  - A FeNO ≥35 ppb with normal spirometry and negative peak flow variability or
  - Obstructive spirometry and positive bronchodilator reversibility

FeNO in the diagnosis of asthma in adults

- Offer a FeNO test to adults (aged >17 years) if a diagnosis of asthma is being considered. **Regard a FeNO level of ≥40 ppb as a positive test**
- Suspect asthma in adults (aged >17) with **symptoms suggestive of asthma**, obstructive spirometry and:
  - Negative bronchodilator reversibility, and either a FeNO level ≥40 ppb, or a FeNO levels between 25 and 39 ppb and positive peak flow variability, or
  - Positive bronchodilator reversibility, a FeNO level between 25 and 39 ppb and negative peak flow variability
- Diagnose asthma in adults (>17 years) if they have symptoms suggestive of asthma and:
  - A FeNO ≥40 ppb with either positive bronchodilator reversibility or positive peak flow variability or bronchial hyperreactivity or
  - A FeNO between 25 and 39 ppb and a positive bronchial challenge test or
  - Positive bronchodilator reversibility and positive peak flow variability irrespective of FeNO level

The current recommendations for using FeNO testing in England as outlined by both NICE and BTS/SIGN is that it be used in those patients where there is diagnostic uncertainty and as an adjunct to spirometry (10, 13) (Box 1). In clinical practice, FeNO is well established as a tool in diagnosing asthma in those patients where there is diagnostic uncertainty.

<u>Can FeNO also identify those patients are more likely respond to corticosteroid therapy?</u>

However, increasing evidence is emerging that high FeNO levels could be a predictor of asthmatic cohorts who have TH2 inflammation (80% of children and approximately 50% of adults, (7-9)) who are more likely to respond to corticosteroid therapy. There is increasing evidence that the combination of high FeNO and high Blood Eosinophil Count (BEC) was associated with significantly increased severe exacerbation rates in the year preceding FeNO reading, suggesting that combining FeNO and Blood Eosinophil Count (BEC) measurements in primary care may identify asthma patients at risk of exacerbations (14). It has also been shown that FeNO levels have been shown to correlate well with sputum eosinophils (16-18), serum eosinophilic cationic protein,22 and immunoglobulin E levels which are also markers for TH2 inflammation (19).

This article will further look into the evidence for the positive and negative predictive value of FeNO for identifying corticosteroid-responsive airway inflammation; and to present the results of an updated meta-analysis, evaluating asthma exacerbation rates with FeNO-based versus clinically based asthma management algorithms (15).

It is well established that FeNO is both a marker of TH2-mediated airway inflammation and also particularly useful as an indicator of Inhaled Corticosteroids (ICS) -responsive airway inflammation and, perhaps more importantly, for identifying airway inflammation that will not respond to corticosteroids. These principles are reflected in the 2011 American Thoracic Society (ATS) guidelines, which recommended the use of normal ranges and clinical cut points when interpreting FeNO values. Specifically, the ATS guide- lines suggest that a FeNO less than 25 ppb (<20 ppb in children) is a strong indicator that responsiveness to corticosteroids is unlikely, while a FeNO greater than 50 ppb (>35 ppb in children) is a strong indicator that responsiveness to corticosteroids is likely (12).

The robust evidence for the positive and negative predictive value (PPV, NPV) of FeNO for identifying corticosteroid-responsive TH2 airway inflammation was reviewed recently by Taylor (20) and his meta-analysis looked at 'Mean ICS dose in patients managed with a FeNO strategy as compared with everyday clinical management' and found;

1. **FeNO has greater value for predicting ICS responsiveness than conventional measures such as peak flow rates, spirometry, and bronchodilator responsiveness (21,22)**
2. **The NPV of FeNO for assessing asthma and identifying ICS non-responsiveness is very high across the asthma studies (91-95%) at cut points of FeNO that generally range from 20 to 30 ppb (21,23)**
3. **The PPV of FeNO for assessing asthma and identifying ICS responsiveness is also high across asthma studies (79-82%) when the FeNO cut point is 47 ppb or higher (22, 24)**

The overall inference being that FeNO using the correct reference ranges (20-30ppb –unlikely to respond to corticosteroids and >47ppb very likely to respond to corticosteroids) is a really good 'point of care' tool in assessing a patients likelihood to respond to corticosteroid treatment.

<u>Can FeNO also be used as a marker of asthma treatment?</u>

Because FeNO levels predict ICS responsiveness, and, more importantly, lack of ICS responsiveness, the ATS guidelines recommend using FeNO in monitoring airway inflammation in patients with established asthma (12). Paradoxically this is because we know when doing FeNO testing one of the false negatives directly correlates to the whether the patient has been using either inhaled or oral steroids prior to the FeNO test.

However, in everyday clinical practice the practitioner should be aware if using the FeNO test as a way of monitoring compliance and adherence of the patient with their corticosteroid inhaler therapy the practitioner needs to consider confounding variables such as:

1. **Chronic rhino-sinusitis may be associated with elevated FeNO levels that may not be responsive to corticosteroid administration (25-27).**
2. **Smoking reduces FeNO levels (11).**
3. **Increased FeNO levels by eating a nitrate- rich diet (12).**
4. **FeNO should be measured before spirometry and bronchodilator administration as both may affect FeNO levels, though the effect is small (12,28).**

Therefore a holistic approach should be taken when interpreting the FeNO result in these patients and not used in isolation. A thorough history and examination be taken to exclude confounding variables and once these have been accounted for and only then the FeNO test is used for monitoring and predicting exacerbation risk.

Summary

Asthma is a chronic disease characterised by airway inflammation and airway hyper-responsiveness, which can clearly be divided into two broad groups those with TH2 inflammation and those with no TH2 inflammation (6). FeNO testing is a quantitative, non-invasive, simple and safe test making it suitable for use in the primary care setting and it use is well established in being used where there is diagnostic uncertainty whether an individual has asthma as set out by NICE/BTS/SIGN and as an adjunct to spirometry (10, 13). However, evidence is emerging that FeNO may have a greater role to play in the management of the asthmatic patient by giving the frontline practitioner the ability to choose a personalised approach to the patient by highlighting which patient will respond to corticosteroid therapy (20) and how well they are complying with the treatment (12).

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