Measurement of FeNO in asthma: what the hospital doctor needs to know

ABSTRACT

Asthma is the commonest chronic lung disease. Airway inflammation is a central component of asthma but clinical symptoms of asthma and standard spirometry are insensitive in reflecting the underlying inflammatory processes. Measurement of the fractional nitric oxide concentration in exhaled breath (FeNO) is a quantitative, non-invasive and safe method of measuring airway inflammation. Advances in technology and standardization have made FeNO measurements simple, enabling their use as a biomarker alongside traditional clinical tools in the assessment and management of asthma. Specifically, it can predict responsiveness to steroids and also newer biological therapy, predict future risk of exacerbation and help highlight treatment non-adherence, making it a useful asset to personalized medicine.

Asthma is the commonest chronic lung disease and is characterized by recurring symptoms resulting from a triad of reversible airflow obstruction, bronchial hyperresponsiveness and airway inflammation (Croisant, 2014). The clinical symptoms of asthma and standard spirometry do not usually reflect the underlying airway inflammation and, if unrecognized, can lead to under-treatment and persistent symptoms. Airway inflammation is categorized as eosinophilic ('T2-high') or non-eosinophilic ('T2-low'), with the former highly sensitive to anti-inflammatory corticosteroid or specific anti-eosinophilic therapy. Nitric oxide is produced by the lungs and the fraction of nitric oxide in exhaled breath (FeNO) is regarded as an indirect marker of this T2-high eosinophilic airway inflammation. Advances in technology and standardization have made FeNO measurements simple, non-invasive and repeatable, allowing quantification of the level of airway inflammation and establishing FeNO as a complementary tool in the diagnosis and management of asthma.

Nitric oxide and airway inflammation in asthma

Airway inflammation in asthma is complex and involves a variety of cytokine mediators and cells. This inflammation is described as T2-high or T2-low according to the level of eosinophils detectable in the airways. T2-high inflammation is orchestrated by a variety of pro-inflammatory cytokines, namely IL-4, IL-5 and IL-13, either by T-helper lymphocyte-dependent mechanisms (e.g. when stimulated by allergens, pollutants and microbes) or T-helper lymphocyte-independent mechanisms (e.g. involving other cell types such as type 2 innate lymphoid and natural killer cells). T2-high asthma occurs in at least 50% of patients with mild-to-moderate asthma (Woodruff et al, 2009) with the proportion higher in those with severe asthma, and if untreated, is linked to specific clinical characteristics of asthma, such as worsening of lung function, poor disease control and increased risk of death. T2-low asthma is less well understood with different levels of non-eosinophilic inflammation characterized by the presence of other cells such as neutrophils, or there may be very few inflammatory cells (paucigranulocytic). This T2-low phenotype is also associated with poor disease control and exacerbations, but currently there are fewer treatment options for this group.

T2-high asthma is generally corticosteroid sensitive and therefore identifying T2-high (or T2-low) asthma has the potential to aid in the diagnosis, guide treatment decisions and monitor responses (Pavord et al, 2017). Bronchial biopsy and sputum induction are considered the 'gold standard' for detecting airway inflammation but they are invasive, costly and technically complex, preventing their widespread use in routine clinical practice. Therefore, over the past few decades, there has been growing interest in identifying easily measurable, surrogate biomarkers for T2-high inflammation.

Nitric oxide has long been known as an air pollutant generated by automotive engines, thermal power plants, and cigarette smoke. Within the airways, nitric oxide is produced at very low levels by constitutive nitric oxide synthases – it functions as a vasodilator, bronchodilator and inflammatory mediator, and has a role in host defence. In cases of airway inflammation, pro-inflammatory cytokines, including IL-4, IL-5 and IL-13, upregulate inducible nitric oxide synthase, producing high levels of nitric oxide (Chibana et al, 2008), making FeNO a surrogate biomarker of T2-high asthma. In the last decade, a number of hand-held devices that measure FeNO has become available advancing it as a point-of-care test in the clinical setting.

Role of FeNO in asthma management

Assist in the diagnosis and identification of asthma phenotypes

Asthma is frequently difficult to diagnose because no one symptom, sign or test is diagnostic, and in practice,

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clinicians rely on a good history and a structured clinical assessment. As a result, it is either over- or under-diagnosed (de São Jose et al, 2014; Aaron et al, 2017). The triad of bronchial hyperreactivity, airway obstruction and airway inflammation are the hallmarks of asthma – these can vary from one individual to another and may be present in varying degrees in the same person. Conventional tests such as peak flow variability and obstructive spirometry rely on the presence of abnormal airway physiology (reflecting bronchial hyperreactivity or obstruction), which may be absent in patients with mild asthma. In contrast, FeNO is reflective of eosinophilic airway inflammation, and in the absence of other point-of-care tests measuring airway inflammation, it is useful when present along with suggestive symptoms in helping to diagnose asthma.

Pros

When using bronchodilator reversibility and bronchial hyperresponsiveness as the gold standard, peak flow measurements, spirometry and changes to these parameters after a trial of steroid have been shown to be poorly sensitive and inferior to FeNO in diagnosing asthma (Smith et al, 2004). FeNO values are both highly sensitive and specific for asthma diagnosis in adults and children, with sensitivities ranging from 0.79 to 0.86 and specificities ranging from 0.85 to 0.89 (Spahn et al, 2016). A systematic review found that the positive predictive value for FeNO is 0.70, which is comparable to those of established bronchial provocation tests (Karrasch et al, 2017).

FeNO is relatively easy to perform compared to conventional tests, even for patients with severe airflow obstruction, children and pregnant women. It involves inhaling to total lung capacity, followed by steady exhalation and flow for 6–10 seconds, with a result available within 1 minute. In contrast, peak flow variability, recommended in international guidelines, relies on patients recording twice-daily serial peak flows over an interval of 14–28 days which is not easily achieved. The forced exhalation required for spirometry assessment can be technically difficult and bronchial hyperreactivity testing is not available in all centres, takes time and requires specialist physiology expertise. It is also not available in primary care, where most patients first receive a diagnosis of asthma. Furthermore, these conventional tests often span numerous consultations, which increases the burden on health-care providers but more importantly for the patient means ongoing symptoms and risk of exacerbation.

Cons

FeNO is a marker of T2 airway inflammation alone and therefore will not detect T2-low asthma. Levels of FeNO generally (but not always) reflect lower airway eosinophilic inflammation. It compares favourably to assessing eosinophils in induced sputum, which is a time-consuming test using hypertonic saline and is available only in specialist centres (Berry et al, 2005; Korevaar et al, 2015). At FeNO levels ≥42 parts per billion, there is a positive predictive value of 74% for sputum eosinophilia of >3%, the accepted cut-off for airway eosinophilic inflammation by sputum cell count (Wagener et al, 2015). Thus, in a small number of patients, especially those with severe asthma, other measures of lower airway inflammation may be required when FeNO levels are normal but eosinophilic inflammation is still suspected. However, even where sputum induction is available, there is a failure rate of up to 37% and an 8% risk of bronchospasm (Covar et al, 2004).

What do national and international guidelines say?

In November 2017, the National Institute for Health and Care Excellence published guidance on the diagnosis of asthma which positioned FeNO prominently in the diagnostic algorithm. The guidance recommends using a FeNO of 40 parts per billion or more in adults to help diagnose asthma in addition to a detailed history and spirometry. However, this emphasis on FeNO is not reflected in other international asthma guidelines. The British Thoracic Society and Scottish Intercollegiate Guidelines Network (2016) guidance lists FeNO as a 'potentially' useful test, specifically in patients with an intermediate probability of asthma and without spirometric evidence of airflow obstruction. The Global Initiative for Asthma (2018) guidelines do not recommend FeNO for asthma diagnosis but recognize that FeNO-guided treatment can lead to significantly fewer exacerbations than treatment based on current guidelines. Global Initiative for Asthma concludes that in patients with a suspected diagnosis of asthma, FeNO can support the decision to start inhaled corticosteroids, but cannot safely be recommended for deciding against treatment with inhaled corticosteroids.

The evidence base considered by the British Thoracic Society/Scottish Intercollegiate Guidelines Network and National Institute for Health and Care Excellence guideline development groups was broadly the same, but the National Institute for Health and Care Excellence methodology is based on health economic modelling. A health technology assessment found that inclusion of FeNO measurement into the diagnostic pathway increases the diagnostic cost effectiveness (Harnan et al, 2015) and could save the NHS at least £10 million over a 5-year period, through reducing unnecessary prescriptions (Wise, 2017). However, the level of 40 parts per billion chosen by the National Institute for Health and Care Excellence remains controversial as cut-off values of >46 parts per billion or 76 parts per billion would provide positive predictive values of 80% and 100% respectively (Schneider et al, 2009).

Use in secondary care

So, should FeNO be used to diagnose asthma? The literature suggests it has a higher specificity than sensitivity, making it a good tool for ruling in asthma, rather than ruling out asthma. FeNO is now an essential part of the systematic evaluation of patients in specialist-led asthma clinics and should be used alongside a careful history, conventional

CASE STUDY 1

Mr LD, a 56-year-old accountant with a 12-pack year smoking history (ex-smoker), was referred to the authors' asthma clinic in August 2016 with a 5-year history of worsening breathlessness and cough. His GP had started tiotropium (a long-acting anti-muscarinic inhaler) with minimal effect – he was having to use his salbutamol reliever 4–5 times a day, and he had required three courses of steroids and antibiotics over the previous 9 months to treat 'chest infections'. On examination, he had bilateral wheeze. His fractional nitric oxide concentration in exhaled breath (FeNO) was markedly raised at 191 parts per billion and his spirometry showed airway obstruction with >15% reversibility in forced expiratory volume in 1 second. He was diagnosed with asthma, given a course of steroids and commenced on a combined beclomethasone/formoterol inhaler (Fostair 100/6) and montelukast.

When reviewed 8 weeks later his symptoms had somewhat improved but he still reported waking most nights to use his reliever inhaler. His FeNO remained elevated, although it had decreased to 86 parts per billion. His inhaled corticosteroid dose was increased to 1600 mcg beclomethasone equivalent and his inhaler technique optimized. On this treatment 8 weeks later, his symptoms improved and his FeNO had reduced to 38 parts per billion. He subsequently felt so well, he stopped his inhaled corticosteroids and montelukast and predictably, when seen in February 2017, his asthma symptoms had worsened, he reported a further exacerbation and his FeNO increased to 96 parts per billion. Both treatments were then restarted and he continues on that regimen with good control of symptoms and no further exacerbations.

Learning points

- The initial raised FeNO helped diagnose asthma that was likely to respond to corticosteroids, confirmed by his subsequent clinical improvement with treatment.
- The persistently high FeNO at the second clinic visit guided the step-up of inhaled corticosteroid therapy and prompted the authors to address his inhaler technique.
- This led to an improvement in symptoms and a corresponding decline in FeNO.

spirometric testing with bronchodilator reversibility, measures of bronchial hyperreactivity using bronchial provocants such as methacholine and other measures of eosinophilic inflammation such as an eosinophil cell count in peripheral blood (Wagener et al, 2015). *Case study 1* illustrates the utility of FeNO in diagnosis, identifying T2-high asthma and titrating anti-inflammatory treatment to improve symptoms and reduce exacerbation risk.

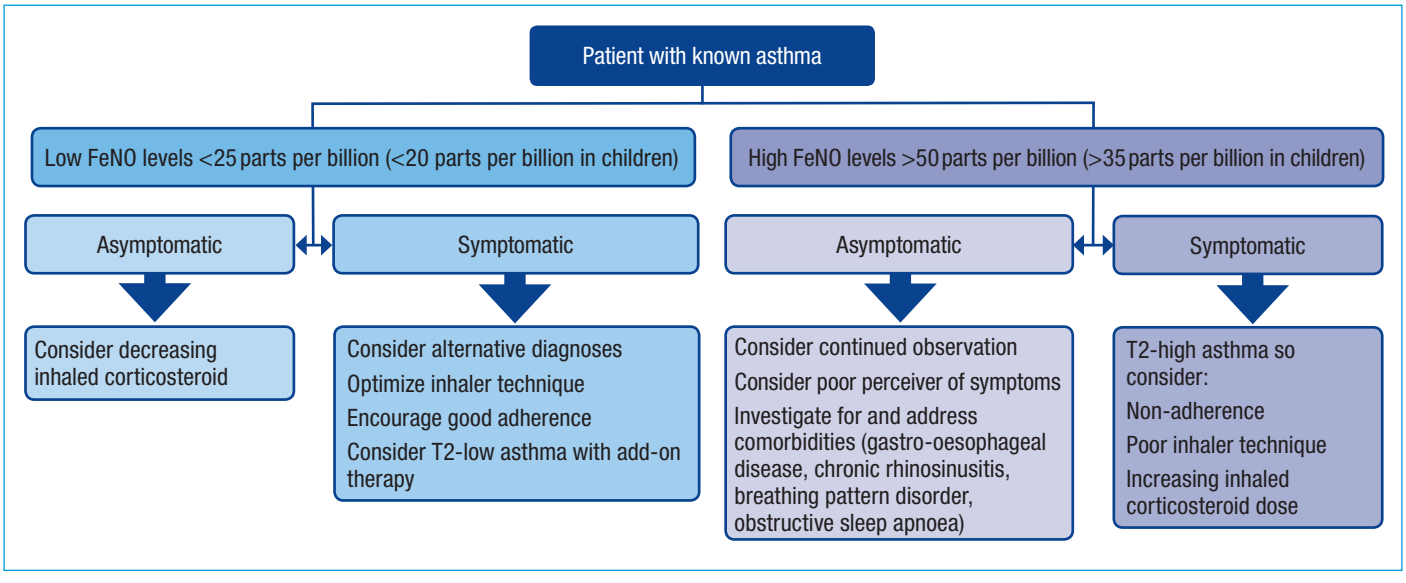
Optimize the dose of inhaled corticosteroids, assess adherence and identify risk

Uncontrolled T2-high inflammation leads to greater rates of severe asthma exacerbations (Kupczyk et al, 2014), thus FeNO targeted treatment would intuitively lead to reduced exacerbations. This has been confirmed in a recent systematic review (Petsky et al, 2018), even though the evidence as to whether it leads to overall lower doses of inhaled corticosteroids compared to conventional approaches remains controversial. It is arguable that using overall dose of inhaled corticosteroids as an outcome measure in FeNO-guided longitudinal studies is imperfect because a lower dose of inhaled corticosteroid in those with low FeNO is offset by much higher doses of inhaled corticosteroid in those with high FeNO. However, reducing exacerbations does lead to reduced systemic corticosteroid exposure, which may matter more to patients. The heterogeneity in response to inhaled corticosteroids in current guidelines can thus in part be explained by those with no eosinophilic inflammation deriving less benefit, up to 45% in one report (Spahn et al, 2016). FeNO may also be useful in stepping down inhaled corticosteroid treatment in those with eosinophilic asthma that is controlled and where FeNO levels have returned to normal. This personalized approach may prevent patients from being committed to steroid therapy inappropriately or at doses higher than needed.

Use in secondary care

A FeNO-guided treatment approach in a secondary care clinic will allow treatment adjustment in those with established T2 high asthma whose symptoms remain controlled or uncontrolled (*Figure 1*). For example, in

Figure 1. Fractional nitric oxide concentration in exhaled breath (FeNO) testing algorithm for an asthma clinic.



symptomatic patients already on inhaled corticosteroid, a raised FeNO would prompt an assessment of dose, inhaler technique and adherence to therapy (*Case study 2*). In symptomatic patients with low FeNO, strategies other than increasing the dose of inhaled corticosteroid should be pursued and greater attention given to addressing coexisting comorbidities such as reflux disease, breathing pattern disorder and psychological conditions. The main issue that remains is identifying reliable cut-off points for FeNO for titrating treatment up or down. Given the heterogeneity of asthma, the optimal approach would be to personalise cut-off points based on an individual's FeNO response to initial inhaled corticosteroid therapy. This would allow the identification of specific cut-off points for that individual and tailoring of treatment based on FeNO variation (Shaw, 2018).

Up to 10% of adults with asthma have 'difficult asthma' which refers to ongoing symptoms and/or exacerbations despite prescription of high dose inhaled corticosteroids in addition to other maintenance therapies (i.e. Global Initiative for Asthma steps 4 and 5), and are increasingly assessed for expensive biological therapies. Non-adherence to inhaled corticosteroids is a major contributing factor to treatment failure in asthma with some estimates suggesting it could be as high as 65% (Gamble et al, 2009), thus identifying that adherence is an essential part of asthma management. Adherence can be identified in a variety of ways including prescription refills, use of Bluetooth-enabled smart inhalers or measures of the adrenocorticotrophic axis in those on maintenance steroids.

Given that FeNO levels decrease within days after inhaled corticosteroid treatment in a dose-dependent fashion, and increase after steroid withdrawal (Kharitonov et al, 2002), a 'FeNO suppression test' could also objectively identify non-adherence (McNicholl et al, 2012). It involves directly-observed inhaled corticosteroid therapy for 7 days along with daily FeNO measurements, with a drop in FeNO at the end of the week indicating non-adherence. It is particularly useful in those patients who collect prescriptions for inhaled corticosteroids but do not take the medication, and where expensive biologic therapies are being considered. However, implementing widespread use of directly-observed inhaled corticosteroid therapy within asthma services has significant resource implications and currently most hospitals cannot routinely offer it.

Personalize biologic therapy in severe asthma

As a biomarker of T2 inflammation, FeNO can guide the dose of inhaled corticosteroid therapy and reduce asthma exacerbations (Petsky et al, 2016, 2018). However, in the difficult-to-treat asthma patient, in whom the uniform approach of increasing the does of inhaled corticosteroids has already been attempted, a persistently raised FeNO can also guide the use of targeted therapies. Omalizumab was the first monoclonal antibody used in asthma and its use in patients with allergic asthma reduces exacerbation rates and hospitalizations, and improves symptoms and quality of life (Normansell et al, 2014). Although high serum IgE levels are used for selecting patients for omalizumab, a higher FeNO at baseline also identifies the most responsive patients (Hanania et al, 2013). Although FeNO is generally accepted as a marker of eosinophilic airway inflammation, it is not helpful in predicting response to mepolizumab, an anti-IL5 therapy (Pavord et al, 2012). In fact, in patients treated with mepolizumab, marked reduction in eosinophils is seen without a parallel reduction in FeNO levels (Haldar et al, 2009), reflecting the role of the IL-4/IL-13 pathway in inducing inducible nitric oxide synthase. Therefore, in patients treated with dupilumab, which targets the IL-4/IL-13 pathway, FeNO is able to predict treatment response and patients with a higher FeNO having the greatest reduction in exacerbations (Castro et al, 2018).

Use in secondary care

If FeNO remains high and control inadequate despite high dose inhaled corticosteroid therapy, treatment of comorbidities and adherence is confirmed, then the patient should be referred to a severe asthma centre for consideration for biological therapy. Alongside the clinical history and other biomarkers, such as peripheral blood eosinophils, FeNO is then used to guide the selection of the most appropriate biological therapy.

CASE STUDY 2

Mrs JK, a 61-year-old housewife, was reviewed in the authors' asthma clinic in October 2016 having not been reviewed for over 18 months as a result of poor clinic attendance. She reported daily asthma symptoms, frequent exacerbations and had required 10 courses of prednisolone in the previous 12 months. Her medications included Fostair 100/6, montelukast and tiotropium Respimat.

Investigations showed a raised fractional nitric oxide concentration in exhaled breath (FeNO) at 94 parts per billion and markedly obstructive spirometry with forced expiratory volume in 1 second:forced vital capacity ratio of 52%. Her electronic prescription records suggested poor adherence, which she admitted to, and her inhaler technique was suboptimal. Some time was spent discussing the importance of adherence and showed her how to use her inhalers. Her treatment was not changed at this visit.

When reviewed 8 weeks later her FeNO remained elevated at 99 parts per billion and she reported a further exacerbation requiring steroids. Her inhaled corticosteroid dose was increased to Fostair 200/6 and once again the importance of adherence was discussed.

She did not attend her next two clinic appointments, but the authors did receive correspondence from her GP expressing concern about her ongoing exacerbations and need for steroid courses. In May 2017, she had a life-threatening asthma attack requiring mechanical ventilation. Since then she has attended clinic regularly, her symptoms are much improved, FeNO normalized to between 20 and 30 parts per billion and self-reported adherence improved. She has had no further exacerbations.

Learning points

- In addition to indicating steroid-responsive disease, the raised FeNO is the result of treatment non-adherence.
- Raised FeNO also predicts an increased risk of exacerbation as seen with this patient's life-threatening asthma attack.
- Once her adherence improved, her symptoms and FeNO improved in parallel.

KEY POINTS

- Fractional concentrated of exhaled nitric oxide (FeNO) is a quantitative, non-invasive and safe method of measuring airway inflammation and is an indirect marker of T2-high eosinophilic airway inflammation in asthma.
- The use of FeNO has a role in aiding asthma diagnosis, predicting steroid responsiveness, preventing exacerbations by guiding medication dosage and assessing adherence.

Conclusions

Routine use of FeNO, in conjunction with conventional clinical measures and lung function tests, can help in the diagnosis and management of asthma. It can predict and tailor responsiveness to inhaled corticosteroid and also newer biological therapy, predict future risk of exacerbation and help highlight treatment non-adherence, making it a useful asset to personalised medicine. **BJHM**

Conflict of interest: none.

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