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Early View

Review

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Clinical utility of fractional exhaled nitric oxide (FeNO) in severe asthma management

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Take home message: The optimisation of FeNO testing methods in a variety of clinical settings, as a non-invasive, readily available, and affordable technology, could play an important role in advancing effective asthma control.

ABSTRACT

Asthma is a chronic inflammatory disease of the airways, affecting over 350 million people worldwide and placing a significant burden on healthcare providers and wider society. Approximately 5–10% of asthma patients are diagnosed with severe asthma and typically are associated with increased risk of hospitalisation from exacerbations, increased morbidity, mortality and higher asthma-associated healthcare costs. Nitric oxide (NO) is an important regulator of immune responses and is a product of inflammation in the airways that is over-produced in asthma. Fractional exhaled NO (FeNO) is predominantly used as a predictor of response to inhaled corticosteroids (ICSs), to monitor adherence and as a diagnostic tool in ICS-naïve patients. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines recommend the use of FeNO for the initial diagnosis of patients with suspected asthma. In the US, the American Thoracic Society (ATS) guidelines recommend FeNO as part of the initial diagnosis of asthma and for monitoring of airway inflammation. FeNO has also been shown to be a predictive factor for asthma exacerbations, with higher levels being associated with a greater number of exacerbations. In addition, higher levels of FeNO have been shown to be associated with a decline in lung function. FeNO testing is a cost-effective procedure and has been shown to improve patient management when combined with standard assessment methods. Recent evidence suggests that FeNO may also be useful as a surrogate biomarker for the assessment and management of severe asthma and to predict responsiveness to some biological therapies.

Keywords: asthma, biomarkers, diagnosis, fraction of exhaled nitric oxide, FeNO, inhaled corticosteroids, management, monitoring, severe asthma

Introduction

Asthma is the most common chronic respiratory disease worldwide, with over 350 million people affected [1], resulting in significant economic and societal burdens [2, 3]. Severe asthma, which is associated with increased morbidity, risk of hospitalisation from exacerbations and increased risk of mortality, affects approximately 5–10% of asthma patients [4–6], and it generates greater healthcare costs than mild or moderate asthma [7–9].

The international European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as "asthma that requires treatment with high-dose inhaled corticosteroids (ICSs) plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy" once the diagnosis of asthma has been confirmed and any comorbidities have been addressed [4]. Poor adherence to treatment, persistent triggers and comorbidities (*e.g.* chronic rhinosinusitis, gastro-oesophageal reflux disease and obesity) often contribute to severe asthma [10].

Although heterogeneous in nature, type 2 inflammation-driven asthma (type 2 asthma) is prevalent, affecting a high proportion of children and approximately 50% of adults with asthma overall and up to 80% of corticosteroid-naïve patients [11–14]. Indeed, these figures may underestimate the true prevalence of type 2 asthma due to the suppressive effects of corticosteroid treatment on type 2 biomarkers [11, 13], and there is some evidence suggesting that almost all patients with asthma will have an element of type 2 disease [14].

Type 2 cytokines such as interleukin (IL)-4, IL-5 and IL-13 play an important role in type 2 asthma. These cytokines are often produced in response to the recognition of allergens by the adaptive immune system but may also be activated by bacteria, viruses and allergens through the innate immune system [15]. Severe type 2 asthma is often associated with increased eosinophilic infiltration, raised serum immunoglobulin E (IgE) and raised fractional exhaled nitric oxide (FeNO) levels [16]. The peripheral blood eosinophil (PBE) count is frequently used as a biomarker to predict the response to treatment in patients with type 2 asthma. In the UK, the Medical Research Council

(MRC) is funding the Refractory Asthma Stratification Programme (RASP-UK), which will explore novel biomarker stratification strategies in severe asthma, with the aims of improving the clinical management of patients and accelerating the development of new therapies [17].

Nitric oxide and type 2 inflammation

There is increasing evidence that nitric oxide (NO) plays a key role in modulating type 2 inflammation and in regulating type 2 immune responses [18]. NO is derived endogenously from the amino acid L-arginine in a synthesis catalysed by three forms of the enzyme NO synthase (NOS); two constitutive NO synthases (cNOS) – generally expressed in platelets, neuronal, epithelial and endothelial cells – are involved in physiological regulation of airway function. An inducible form of the enzyme (iNOS) – predominantly expressed in macrophages, neutrophils, hepatocytes and epithelial, mesangial, endothelial and vascular smooth muscle cells – is typically produced in response to airway inflammation and in host defence against infection (figure 1) [19, 20]. iNOS expression can be induced by proinflammatory cytokines, such as tumour necrosis factor α, interferon γ and IL-1β [20]. In addition, it has been suggested that IL-13 upregulates the iNOS gene and protein expression in epithelial cells, leading to increased levels of FeNO [21, 22].

NO is a ubiquitous messenger molecule, the activity of which depends on the level of oxidant stress and the rate of uptake by antioxidant molecules, in addition to the amount and activity of NOS [20]. NO regulates various biological functions – either at low concentrations as a signal in many physiological processes, including platelet reactivity, blood flow, non-adrenergic non-cholinergic neurotransmission and neurological memory, or at high concentrations as cytotoxic and cytostatic defensive mechanisms against tumours and pathogens [23]. NO is also a key inflammatory mediator in the respiratory tract and is produced by a number of cell types, including epithelial cells, mast cells, macrophages, neutrophils and vascular endothelial cells. Evidence highlights several roles for NO in the regulation of pulmonary function and in pulmonary disease, as an endogenous modulator of airway function and as a proinflammatory and immunomodulatory mediator [20].

In the context of asthma, this inflammatory response is deleterious, resulting in increased symptoms and airway obstruction [20, 24]. Increased levels of exhaled NO in asthma, originating mainly from the lower airway, are often associated with airway eosinophilic inflammation and increased expression of corticosteroid-sensitive iNOS. Levels of exhaled NO may also be associated with exacerbations and disease severity [20].

The measurement of exhaled NO has now been standardised for clinical use and, facilitated by the availability of mobile technology and remote monitoring, and adoption in general practice has increased in recent years [25–27]. FeNO testing is relatively convenient to perform, with numerous studies providing evidence of the applications of NO measurement in clinical practice [28,29]. Currently, FeNO measurements are used to predict and document the response to ICSs [30], to monitor adherence [26, 31] and as a diagnostic tool in ICS-naïve patients [28].

In this review, we discuss the current uses of FeNO, its utility in the prediction of future exacerbation risk, the relationship between FeNO and other biomarkers of inflammation in severe type 2 asthma and the potential use of FeNO in patient selection/stratification for personalised treatment.

The association between FeNO and other measures of airways inflammation

Biomarkers of type 2 inflammation include serum IgE, blood or sputum eosinophils, FeNO and serum periostin [16]. Measurement of eosinophil numbers in induced sputum and from bronchial biopsy is considered the “gold standard” for identifying underlying type 2 airway inflammation (and thereby aiding identification of a type 2 asthma phenotype). However, bronchial biopsy is an invasive procedure with significant short-term morbidity. It also requires a dedicated facility and considerable laboratory support to maximise the information from the material sampled, which limits its use in routine clinical practice [29, 32]. Sputum analysis, while well tolerated, must be performed in laboratories with relevant expertise, is relatively time-consuming and is not always successful (with reported success rates ranging from 74% to 94%), leading to bias in reporting [33–39]. FeNO adds an additional dimension to traditional clinical testing, with advantages including the non-invasive

nature of the test, the ease of repeat measurements and its relatively simple use in patients with severe airflow obstruction, where other techniques may be difficult to perform [40].

FeNO has been shown to have comparable accuracy to peripheral blood eosinophilia in predicting sputum eosinophilia in adults with asthma, irrespective of factors such as severity, degree of atopy and smoking status [41]. In addition, FeNO levels correlate well with the level of inflammation and decrease in response to ICS treatment [42]. However, whilst ICS treatment is a strong suppressor of FeNO [43], its effect on PBEs is probably weak [44]. Conversely, treatment with oral corticosteroids (OCS) appears to have more influence on PBEs than on FeNO [45].

Although FeNO generally correlates with eosinophilia, this is not always the case, as FeNO and eosinophilia result from inflammatory processes that involve different type 2 cytokine pathways; the relative production of the corresponding cytokines determines the level of each biomarker [42]. While cytokines IL-4 and IL-13 are involved in regulating IgE synthesis and increasing FeNO levels, IL-5 is the main cytokine involved in the development, recruitment and activation of eosinophils. This supports the concept that FeNO should not be considered a surrogate marker for sputum eosinophils but rather a parallel marker of airway inflammation often, but not always, associated with eosinophilia [42, 46–48].

Measuring both FeNO levels and blood eosinophil counts may provide more information than using either alone, as they are both valid, but distinct, biomarkers for type 2 inflammation [49–52]. It has been suggested that both FeNO levels and blood eosinophil counts should be incorporated in future diagnostic algorithms [53]. There is also some evidence that simultaneously increased FeNO levels and blood eosinophil counts are associated with a higher prevalence of uncontrolled asthma and moderate-to-severe bronchial hyper-responsiveness [50]. In a retrospective study of patients with severe asthma, the combined analysis of FeNO levels and blood eosinophil counts identified patients with frequent severe exacerbations, which the authors concluded may help in formulating therapeutic strategies for comprehensive asthma control [52].

FeNO and exacerbations

FeNO is a predictive factor for asthma exacerbations, with increased levels of FeNO being associated with a higher number of exacerbations [54–56]. Several systematic reviews of asthma management trials have shown that tailoring asthma medications based on FeNO levels significantly reduces future exacerbation risk [57–60]. In a meta-analysis that compared the use of FeNO to guide treatment with management based on clinical symptoms or asthma guidelines or both, the number of adults who had one or more asthma exacerbations was significantly lower in the FeNO-guided group than in the control group (odds ratio [OR] 0.60) [59]. However, there was no statistically significant difference between the groups for exacerbations requiring hospitalisation (OR 0.14) or rescue OCS (OR 0.86).

In a similar comparative analysis in children, the number of children having one or more asthma exacerbations was significantly lower in the FeNO-guided group than in the control group (OR 0.58) [58]. As in the adult meta-analysis, there was no statistically significant difference between the groups for exacerbations requiring hospitalisation (OR 0.75) [59]. Furthermore, FeNO has been shown to be more strongly correlated with exacerbations than PBE counts (r=0.42; p=0.0008 *versus* r=0.34; p=0.0078) [56]. However, there was high prevalence of the use of OCS (56% of patients) in this study, which might have suppressed the PBE signal more than the FeNO signal.

In a study using National Health and Nutrition Examination Survey (NHANES) data (2007–2008 and 2009–2010), FeNO and blood eosinophil values provided independent information on the prevalence of current asthma, the occurrence of asthma events and the prevalence of wheeze [49].

FeNO and lung function

Higher levels of FeNO have been shown to be associated with a decline in lung function [61–64]. In a prospective 5-year follow-up study of 200 adults with newly diagnosed asthma, high FeNO levels (≥57 ppb) were associated with a more rapid decline in lung function [61]. In a 3-year prospective study in Japanese adults with stable, controlled asthma [62], FeNO levels >40.3 ppb were shown to

have 43% sensitivity and 86% specificity for identifying patients with a rapid decline in forced expiratory volume in 1 second (FEV_1). In a study of Korean children with atopic or non-atopic asthma, higher FeNO levels were associated with reduced lung function in children with atopic asthma [63]. High FeNO levels (≥20 ppb) were associated with worse lung function in children and adolescents aged 6–18 years with persistent asthma compared with those who had low FeNO levels (<20 ppb) [64].

In a study of patients included in the NHANES (2007–2012), combined high FeNO levels and blood eosinophil counts identified patients with a higher risk of reduced lung function and wheezing symptoms [51].

Clinical utility of FeNO measurements

The role of FeNO in asthma diagnosis

Current National Institute for Health and Clinical Excellence (NICE) guidelines in the UK recommend the use of FeNO for the initial diagnosis of patients with suspected asthma [28]. NICE standards for a positive FeNO test are >40 ppb in adults and >35 ppb in children (5–16 years) (table 1) [28]. However, the pre-test probability of asthma will impact on subsequent clinical decision-making with regards to the FeNO measurement. A single positive test in isolation is insufficient to make a diagnosis of asthma, irrespective of the pretest probability, and additional bronchial provocation testing can be beneficial to determine airway hyper-responsiveness [28].

The recently published Scottish consensus statement on the role of FeNO in adult asthma suggests cut-off values for FeNO of >40 ppb in adult patients who are ICS naïve to support asthma diagnosis and FeNO >25 ppb for adult patients taking ICSs [65]. In the Global Initiative for Asthma (GINA) report [15], ≥20 ppb FeNO in conjunction with other characteristics, such as blood eosinophils ≥150 cells/μL and/or sputum eosinophils ≥2%, could indicate patients with type 2 immune response (table 1).

FeNO measurement is also recommended by the ATS as part of the initial diagnosis of asthma and for monitoring of airway inflammation [40]. The ATS guidelines define high, intermediate and low FeNO levels in adults as >50 ppb, 25–50 ppb and <25 ppb, respectively. In children, high, medium and low FeNO levels are classified as >35 ppb, 20–35 ppb and <20 ppb (table 1) [40]. The ATS guidelines further advise against the use of reference values derived from a "normal" population when interpreting FeNO levels, as the distribution of FeNO in an unselected population is skewed such that the upper limits overlap with the range of values obtained in populations with asthma [40]. One immediate observation to be made from the various guideline cut-offs is the range of values adopted, which might reflect differences in the evidence base used to arrive at the chosen thresholds, but nevertheless appear arbitrary. The use of fixed cut-off levels is problematic, since (as discussed in the Limitations section) FeNO can be influenced by a number of factors unrelated to the disease. The absence of evidence-based, patient-adjusted cut-offs has been cited as one of the remaining unresolved issues with FeNO measurement [53]. A joint European Respiratory Society-Global Lung Function Initiative task force is currently developing subject-specific FeNO values [66], as have been successfully achieved previously for spirometry, lung volumes and diffusion capacity [67, 68].

FeNO as a predictor of treatment response

A FeNO level >50 ppb in adults is a strong indicator that the patient is likely to be responsive to ICS therapy [69]. In an observational, single-centre study conducted at an outpatient asthma and allergy specialty clinic in the US, treatment decisions were first based on the results of symptoms, clinical examination and spirometry, then any treatment changes based on FeNO measurements were documented [70]. Without FeNO measurement, the physician's assessment of airway inflammation was incorrect in 50% of patients, and FeNO measurement substantially altered the treatment decisions in 36% of patients. In another real-world study involving 337 specialist asthma practices in the US that investigated the impact of FeNO measurement on asthma management, FeNO

measurement enabled doctors to assess underlying airway inflammation, which led to a significant revision of the treatment plans compared with clinical assessment alone [71]. The clinical assessment agreed with FeNO measurement in only 56% of cases. After FeNO measurement, doctors altered the treatment plan in 31% of cases and changed ICS prescriptions in 90% of cases [71].

In a randomised controlled study conducted primarily in the UK, a significant interaction was observed between FeNO levels at baseline and treatment groups (ICSs *versus* placebo), indicating the magnitude of treatment response depends on the FeNO level at baseline [30]. For every 10-ppb increase in baseline FeNO, the change in the Asthma Control Questionnaire (ACQ-7) mean score increased by 0.071 (p=0.044) more in the patients using ICS than placebo. Baseline FeNO also had a strong association with improvement in cough severity in this study, with higher FeNO values associated with greater odds of a clinical response, defined as an improvement of 20 mm or more on the visual analogue scale for cough symptoms [30]. A UK observational study assessing the ability of FeNO to diagnose asthma and predict response to ICS therapy concluded the true utility of the FeNO test to be in detecting the presence of underlying T2 inflammation, identifying patients in whom ICS response is highly unlikely, thus guiding the appropriate use of ICSs in asthma treatment [72].

The use of FeNO to guide asthma management in pregnant women appears to be as effective, if not more so, than in other adults [73]. In a double-blind, randomised trial of inflammatory marker-based management of asthma in pregnancy, a treatment algorithm based on FeNO level and ACQ score led to a significant reduction in asthma exacerbations and less use of β2 agonists compared with a clinical algorithm. Although the study was not specifically powered to assess perinatal outcomes, FeNO-guided management resulted in a normalisation of babies' birthweights, and reduced rates of neonatal admissions and preterm deliveries (both of which are increased in asthmatic pregnancies) [73]. Although further studies are needed, there is some evidence that FeNO has the potential to be a useful and cost-effective tool for titration of ICS dose and in guiding management of asthma therapies [59, 74-77].

FeNO and adherence to therapy

FeNO has been used to monitor adherence to ICS therapy, as persistently high FeNO levels can be an indication of non-adherence [26, 40, 43]. In a study of patients with "difficult asthma", defined as patients who remained symptomatic despite treatment at GINA steps 4 and 5, a FeNO suppression test differentiated patients who were adherent or non-adherent to ICS treatment. After 7 days of directly observed ICS (DOICS) treatment, non-adherent patients experienced a significantly greater reduction from baseline in FeNO levels compared with adherent patients (52.4% *versus* 20.4%; $p<0.003$) (figure 2) [43]. A rapid fall in FeNO after DOICS treatment can therefore identify patients who are presumed to have refractory disease but are actually not receiving optimal ICS treatment [43]. In a recent study in severe asthma centres in the UK, an FeNO suppression test delivered using remote monitoring technology was shown to be a simple and effective method to identify which patients were adherent to, and those who derived benefit from, ICS/long-acting β_2-adrenergic receptor agonist (LABA) treatment [26].

FeNO as a biomarker in severe asthma

Severe asthma is a heterogeneous disease and can be divided into several phenotypes according to inflammatory, clinical and functional characteristics [78]. These phenotypes may have prognostic value and therapeutic implications. The pathophysiology of severe asthma is poorly understood, and it is therefore difficult to treat. However, from our current understanding of type 2 inflammation and the importance of its components to the pathophysiology of asthma, several key factors have been identified, including IgE, eosinophils and the IL-4/IL-13 pathway.

To help select appropriate biologics for severe asthma, a limited number of biomarkers are currently available, including IgE, PBEs and FeNO, each of which reflects the characteristics of the underlying inflammatory profile and specifically the presence of type 2 inflammation [5, 79, 80]. Periostin has

also been validated as a marker of type 2 inflammation although with limited clinical use as its levels are influenced by bone metabolism [79].

High FeNO levels in severe asthma have been shown to identify patients with greatest airflow limitation and reversibility, highest sputum eosinophil counts, and most emergency department visits and intensive care unit admissions, suggesting that grouping patients with severe asthma by FeNO identifies the most aggressive asthma phenotype [81].

Biomarker-guided management options

A number of monoclonal antibody (mAb)-directed biologics are now available, directed against inflammatory targets, including omalizumab (anti-IgE), mepolizumab (anti-IL-5), reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor α) and dupilumab (anti-IL-4 receptor α) (table 2) [82–91].

Omalizumab, an anti-IgE mAb, was the first biological therapy to be approved as an add-on therapy for adults and children aged ≥6 years with severe persistent allergic asthma which is uncontrolled despite the use of ICS/LABA. Type 2 biomarkers associated with omalizumab efficacy have been investigated in several studies [92, 93].

In an analysis of biomarkers in the EXTRA study, which included patients with uncontrolled severe persistent allergic asthma, high levels of FeNO (≥19.5 ppb), blood eosinophils (≥260 cells/μL) and serum periostin (≥50 ng/mL) were associated with a greater treatment effect of omalizumab on exacerbation frequency, although several other serum biomarkers (specific-to-total IgE ratios, serum tryptase, eosinophil cationic protein or soluble CD23) were unable to predict outcomes with omalizumab [93].

Recently, in the prospective, real-world, PROSPERO study in patients with moderate-to-severe allergic asthma, 87% of patients had a positive treatment response to omalizumab (measured by several parameters), irrespective of baseline biomarker levels of blood eosinophils or FeNO [92]. Therefore, the utility of blood eosinophil and FeNO levels as predictors of treatment outcomes with omalizumab remains uncertain.

Mepolizumab [94–96] and reslizumab [97, 98] are mAbs that target IL-5, and benralizumab [99, 100] is a mAb that targets the IL-5 receptor. They are approved as add-on therapy for inadequately controlled severe refractory eosinophilic asthma in adults (all three agents) and in children aged ≥6 years (mepolizumab). Blood IgE counts, and blood and sputum eosinophil counts, have been used as biomarkers to identify patients for whom treatment is likely to result in clinically significant reductions in exacerbations [5, 47, 101].

Mepolizumab trials employed blood eosinophil cut-offs of ≥150 cells/μL at baseline or ≥300 cells/μL in the 12 months prior to allow inclusion of patients likely to achieve significant clinical benefit [101]. The absence of a pharmacodynamic response in FeNO levels documented in trials with mepolizumab (in contrast to its depleting effect on blood eosinophils) suggests that FeNO is not responsive to modulation through the IL-5 pathway and is potentially more impacted by other aspects of type 2 inflammation (*e.g.* IL-13) [101–103].

However, in a post-hoc analysis [104] of the mepolizumab phase 2b DREAM study [102], patients with high baseline blood eosinophil levels experienced a greater reduction in exacerbations on mepolizumab treatment if they also had high baseline FeNO levels (61%) than if they had low FeNO levels (33%). Negligible reductions were observed in patients with low baseline blood eosinophil levels, irrespective of baseline FeNO levels [104].

Lebrikizumab [90] and tralokinumab [91] are investigational anti-IL-13 mAbs that have completed 52-week, phase 3 trials in patients with uncontrolled asthma. Lebrikizumab did not consistently show significant reductions in asthma exacerbations in patients with high type 2 biomarker levels (periostin ≥50 ng/mL or blood eosinophils ≥300 cells/μL) [90]. Similarly, tralokinumab did not significantly reduce the annualised exacerbation rate compared with placebo in the overall study populations [91]. However, these studies did confirm that FeNO was reduced by anti-IL-13 therapy [105], and the clinical efficacy observed was greater in those patients who had high levels of FeNO, although the magnitude of benefit did not meet primary outcomes.

Dupilumab targets the shared receptor component for IL-4 and IL-13. It is approved in the US as an add-on maintenance treatment in patients with moderate-to-severe asthma in patients aged ≥12 years with an eosinophilic phenotype or with OCS-dependent asthma. It is approved in the EU as an add-on maintenance treatment in patients aged ≥12 years with type 2 severe asthma characterised by increased blood eosinophil and/or raised FeNO levels who are inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment.

In clinical trials, dupilumab significantly reduced FeNO, plus several additional biomarkers of type 2 inflammation (such as IgE). A transient increase in blood eosinophil levels was observed, which decreased close to baseline levels by the end of the treatment period [78, 97]. Raised baseline eosinophils (>150 cells/µL) or FeNO (>25 ppb) were both predictive of greater response to dupilumab, in terms of exacerbation reduction and improved FEV_1, suggesting both biomarkers may be potentially useful for informing treatment decisions and for monitoring biological response in patients with uncontrolled moderate-to-severe asthma [84, 106].

Cost-effectiveness of FeNO measurement

Cost is often cited as a barrier to the use of FeNO. However, FeNO testing has been shown to be a cost-effective procedure [70, 107–111]. FeNO measurement is considered by the NICE in the UK to be cost effective as an option to help diagnose asthma in adults and children, for asthma management in adults and to support symptomatic asthma management in people using ICSs [110]. In a UK cost-effectiveness study, diagnosis of asthma using FeNO was found to cost GBP 43 less per patient than standard diagnostic methods and the use of FeNO measurement for asthma management rather than lung function testing resulted in an annual cost-saving of GBP 341 and 0.06 quality-adjusted life-years (QALYs) gained for patients with mild-to-severe asthma, and an annual cost-saving of GBP 554 and 0.004 QALYs gained for patients with moderate-to-severe asthma [111]. In line with NICE guidelines, the recently published Scottish consensus statement on the role of FeNO in adult asthma also concluded that FeNO can be a cost-effective tool in the diagnosis and

management of asthma [70]. In a retrospective study in the US using data from a Medicare database, FeNO monitoring in patients with a history of exacerbations was associated with a substantial reduction in asthma-related emergency department claims and inpatient admissions [108]. Inpatient or emergency department charges per beneficiary per day were USD 6.46 with FeNO monitoring compared with USD 16.21 before the use of FeNO [108]. In a US decision-tree analysis comparing standard of care alone and in conjunction with FeNO monitoring, the addition of FeNO decreased annual expenditure from USD 2,637 to USD 2,228 per patient and increased expected per-patient annual QALYs from 0.767 to 0.844 *versus* standard of care alone [109]. In a US observational, single-centre study conducted at an outpatient specialty asthma and allergy clinic, use of FeNO in addition to standard of care was estimated to save USD 629 per patient per year [108]. These cost savings in diagnosis, management and treatment optimisation are reflective of the benefits described in the above discussion.

Current limitations

Although FeNO levels are higher in patients with asthma characterised by type 2 inflammation, they can also be elevated in other related conditions, such as eosinophilic bronchitis, allergic rhinitis, atopy and atopic dermatitis [112, 113]. FeNO is also elevated in upper respiratory tract infections and in pulmonary infections of lung transplant patients and sometimes in patients with chronic obstructive pulmonary disease (COPD) [114, 115]. However, the exact role of FeNO in COPD and more specifically for monitoring asthma–COPD overlap (ACO) in patients on ICS therapy is still unclear and needs to be defined. Moreover, the literature defining the role of FeNO and the practical cut-off value in patients with ACO and established COPD is minimal [115].

Currently, FeNO levels are being used to monitor type 2 asthma [38, 58, 59], and the latest GINA guidelines recommend cut-offs for both blood eosinophils and FeNO to help define the type 2 asthma population [15]. However, the GINA guidelines do not recommend the use of FeNO to guide treatment in the general asthma population [15].

FeNO levels can also be affected (positively and negatively) by many other factors [40, 112, 116]. Smoking leads to a decrease in FeNO (although values are still higher in smokers with asthma than in those without) [117]. Studies have also demonstrated an association with height and gender (the latter, however, might be attributable to differences in height). FeNO may also be associated with age: children have lower levels, which increase significantly as they grow up [118], and elderly patients demonstrate elevated levels [117].

Variability of access to FeNO testing can limit its availability. In the UK, for example, testing is ubiquitous in tertiary or specialist centres; however, globally, FeNO measurements are not widely used, with some countries not supporting reimbursement of testing. Therefore, there is a wider need for increased education on the importance of FeNO measurement in asthma management.

Conclusion

Advances in technology and standardisation have simplified the measurement of FeNO, permitting its use as a biomarker in the assessment of inflammatory airway diseases, such as type 2 asthma. Measurements can be performed in a variety of settings and are easily repeatable. FeNO monitoring in routine clinical practice could play a key role in helping doctors to improve the accuracy of diagnoses in patients who have non-specific respiratory symptoms and in identifying those patients more likely to respond to ICS. In addition, there is substantial evidence supporting the use of FeNO for ongoing monitoring. FeNO measurement can help to identify patients who have poor asthma control, those at greater risk of exacerbations and those at risk of progressive loss of lung function. Ongoing patient assessment using FeNO can be beneficial in guiding corticosteroid dosing and monitoring patient adherence to corticosteroid therapy. FeNO levels can also be used to help identify patients with asthma who are likely to benefit from personalised treatments with biological therapies targeting type 2 inflammation. In conclusion, biomarker-based stratification of airway disease towards precision medicine is a reality now, but needs to evolve further with wider adoption. FeNO has significant potential as part of such a biomarker-based approach to the

management of airway disease in primary and secondary care, and the optimisation of FeNO testing methods in a variety of clinical settings as a non-invasive, readily available, and affordable technology will be important in advancing effective asthma control.

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Figures/Tables

FIGURE 1 Nitric oxide metabolism in asthma pathophysiology. cGMP: cyclic guanosine monophosphate; cNOS: constitutive nitric oxide synthase; iNANC: inhibitory non-adrenergic non-cholinergic; iNOS: inducible nitric oxide synthase; nNOS: neuronal nitric oxide synthase; NO: nitric oxide. Reproduced with permission from MEURS *et al.* [19].

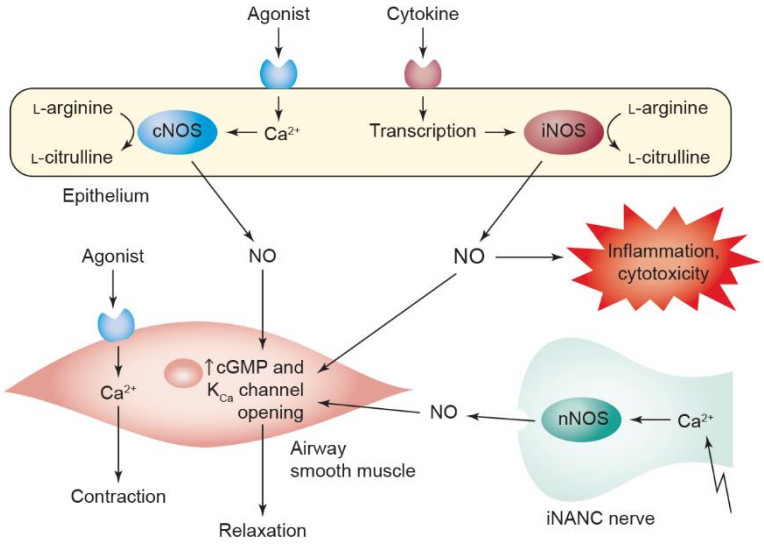

FIGURE 2 FeNO levels in adherent and non-adherent patients on ICS therapy after DOICS treatment. Non-adherent (n = 9; grey circles) and adherent patients (n = 13; black squares). ICS: inhaled corticosteroids; DOICS: directly observed ICS; fractional exhaled nitric oxide; FeNO. Reproduced with permission from McNicholl *et al.* [43].

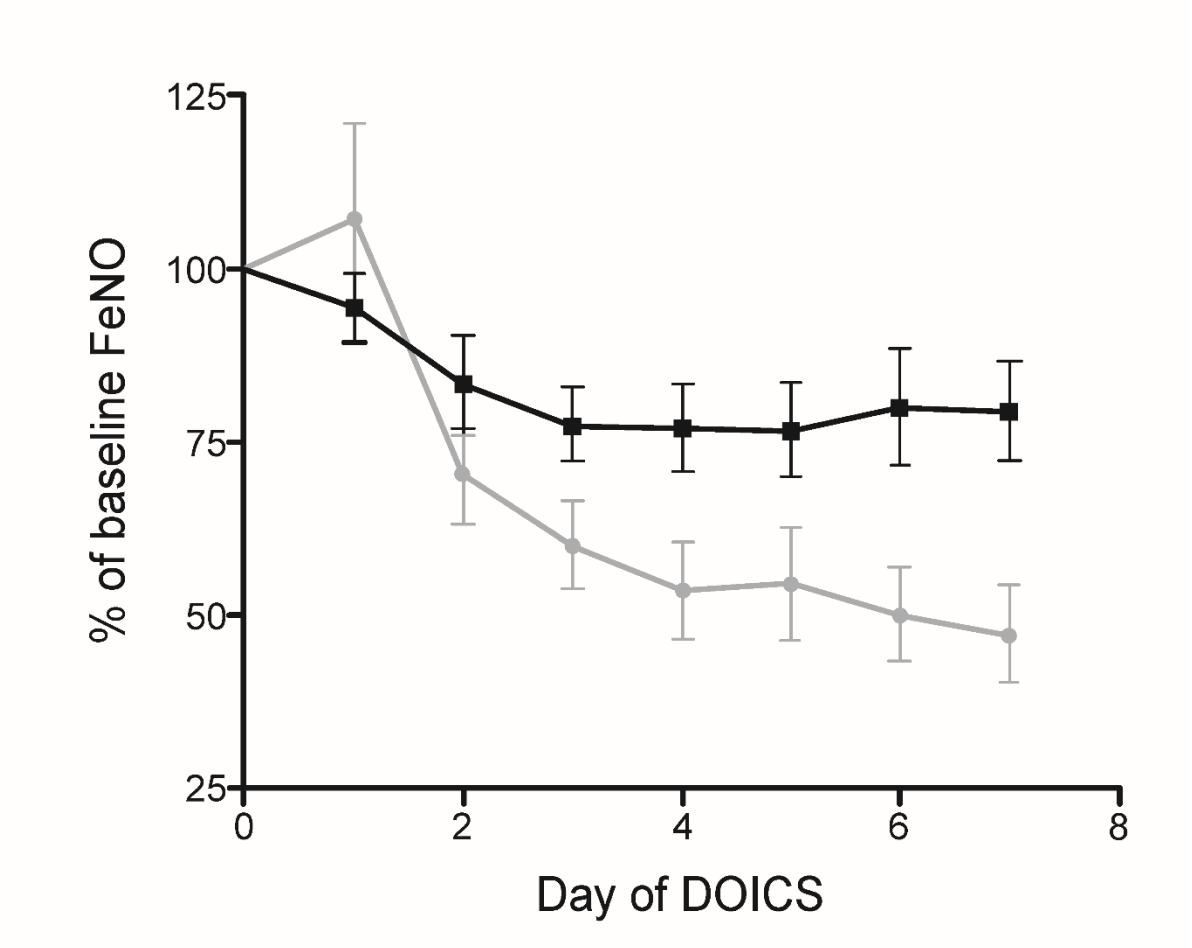

TABLE 1 FeNO cut-offs in different guidelines

Guidelines	FeNO cut-offs	Justification
NICE [28]	***Adults***: • Positive: >40 ppb ***Children (5–16 years):*** • Positive: >35 ppb	
Scottish consensus statement [65]	***ICS-naïve patients*** • >40 ppb ***Patients taking ICS*** • >25 ppb	
GINA [15]	***Adults***: • ≥20 ppb	Associated with eosinophilic inflammation (in non-smokers)
ATS/ERS [40]	***Adults:*** • High: >50 ppb • Intermediate: 25–50 ppb • Low: <25 ppb	Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely Cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely
ATS/ERS [40]	***Children:*** • High: >35 ppb • Intermediate: 20–35 ppb • Low: <20 ppb	Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely Cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely

ATS: American Thoracic Society; ERS: European Respiratory Society; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; NICE: National Institute for Health and Care Excellence.

TABLE 2 Type 2-directed therapies based on monoclonal antibodies: key clinical trials in asthma

Target	Drug	Patient characteristics and biomarkers	Main response
Free IgE	Omalizumab [82, 83]	Severe asthma on ICS/LABA; atopic status, serum IgE 30–1,500 IU/mL (EU Label)	Reduced asthma exacerbations Improved mean AQLQ scores
IL-4Rα	Dupilumab [84]	Moderate-to-severe-uncontrolled asthma; FEV_1 reversibility; persistent symptoms (ACQ-5 ≥1.5); exacerbation in past year	Decrease in asthma exacerbations Improvement in FEV_1 and % change in FEV_1 Reductions in mean ACQ-5 and AQLQ scores
IL-5	Mepolizumab [85, 86]	Severe asthma on ICS and LABA±OCS; blood eosinophils ≥150 cells/μL at screening or ≥300 cells/μL in past year	Reduced exacerbation rates Decrease in maintenance OCS Improvement in FEV_1 Reductions in ACQ-5 and SGRQ scores
IL-5	Reslizumab [87]	Inadequately controlled moderate-to-severe eosinophilic asthma (≥400 cells/μL during screening; ACQ-7 ≥1.5)	Decrease in asthma exacerbations Improvement in FEV_1 Reductions in mean ACQ-7 and AQLQ scores
IL-5Rα	Benralizumab [88, 89]	Severe asthma uncontrolled by medium/high-dose ICS+LABA for ≥1 year; ≥2 exacerbations in previous year (ACQ-6 ≥1.5). Baseline stratification: eosinophils <300 and ≥300 cells/μL	Decrease in asthma exacerbations Improvement in FEV_1 Reduction in maintenance OCS Reductions in mean ACQ-6 and AQLQ scores
IL-13	Lebrikizumab [90]	Not well controlled on ICS/LABA; blood eosinophils; serum periostin	Did not consistently significantly reduce asthma exacerbations in patients with high type 2 biomarker levels Reductions in mean ACQ-5 and AQLQ scores
IL-13	Tralokinumab [91]	Severe uncontrolled asthma despite controller therapies (ACQ-6 ≥1.5)	No significant reduction in exacerbation rate Reductions in mean ACQ-6 and AQLQ scores

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; IgE: immunoglobulin E; IL: interleukin; LABA: long-acting β_2-adrenergic receptor agonist; OCS: oral corticosteroids; SGRQ: St. George's Respiratory Questionnaire.