

2020 Updated Asthma Guidelines: Clinical utility of fractional exhaled nitric oxide (FENO) in asthma management



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Fractional exhaled nitric oxide (FENO) is the only currently available point-of-care test of type 2 inflammation in asthma, being mediated by IL-13 (Fig 1). A Scottish consensus statement emphasized that the role of FENO needs to be considered in the context of a detailed history, spirometry, serial peak flows, allergy testing, eosinophils, and bronchial challenge testing.¹ Here, we critique key aspects of the National Education and Prevention Program (NAEPP) Expert Panel Report 4 Working Group (EPR-4) focused update to the asthma management guidelines, which made some cogent evidence-based recommendations on the utility of FENO in asthma.

A conditional recommendation with a moderate certainty of evidence (COE) was made in regard to diagnostic accuracy of FENO. Values <25 ppb in adults and <20 ppb in children (aged 5-12) are inconsistent with type 2 (T2) inflammation and would suggest a diagnosis other than asthma. The diagnostic accuracy was highest for cutoffs less than 20 ppb in inhaled corticosteroid (ICS)-naïve patients with asthma. It is important to take into account the diurnal variability in FENO with respect to the timing of measurements. For serial domiciliary FENO measurements while taking ICS, the amplitude of diurnal variability was between 24% and 29%, with morning values being higher.² Also, the type of analyzer may influence results. For example, corresponding mean values in children for the NObreath (Intermedical, Aylesford, UK) and NIOX Vero devices (Circassia, Oxford, UK)

were 20 ppb versus 27 ppb, respectively. We would therefore perhaps advise a degree of caution in using a borderline low value with the NObreath device to rule out asthma. Because airway hyperresponsiveness (AHR) is one of the hallmarks of persistent asthma, our practice is to stop ICS for at least 2 weeks prior to performing both FENO and indirect bronchial challenge with mannitol to establish an asthma diagnosis in equivocal cases. Pointedly, the time taken for FENO levels to return back to baseline after stopping fluticasone propionate (FP) and fluticasone furoate is 8 days and 21 days, respectively.^{2,3} Hence, clinicians need to be aware that a longer washout period may be required with fluticasone furoate. In a study of community-diagnosed asthma, those with a positive challenge test result had a mean FENO of 26 ppb (95% CI, 21-32) compared with 16 ppb (95% CI, 13-20) for those with a negative challenge.⁴

A conditional recommendation was made regarding the clinical utility of FENO in selecting controller therapy and monitoring response where COE was low. In this respect, a dose-response study found FP 100 µg/d to result in 84% relative suppression in daily domiciliary FENO compared with FP 500 µg/d.² The mean duration with FP 100 µg/d was 2.9 days and 9.7 days to produce 50% and 90% suppression, respectively, from baseline. In this study, mean (95% CI) asthma control questionnaire (ACQ) values fell from 1.16 (95% CI, 0.79-1.54) to 0.48 (95% CI, 0.24-0.71), whereas asthma quality of life questionnaire value increased from 5.77 (95% CI, 5.37-6.17) to 6.45 (95% CI, 6.20-6.70), amounting to a difference of 0.68 in both, which exceeded minimal clinically important differences of 0.5. Furthermore, there was an accompanying 1.8 doubling dose shift in mannitol airway hyperresponsiveness, which exceeded the biological variability of 1.0 doubling dose. A FENO suppression test with ICS can identify individuals with refractory severe asthma who are nonadherent to ICS, which may be a valuable step before prescribing expensive biologics for such patients. The first consideration clinicians should bear in mind when reviewing a poorly controlled patient with a raised FENO is nonadherence to ICS and associated poor inhaler technique.

Since ACQ and blood eosinophils are strong predictors of future exacerbations,^{5,6} FENO on its own should not be used to stratify risk per se. This point is illustrated by 2 separate studies that identified that FENO greater than or equal to 50 ppb together with blood eosinophils greater than or equal to 300/µL was associated with a 73% (95% CI, 33-89) increased exacerbation risk, whereas FENO greater than or equal to 25 ppb with blood eosinophils greater than or equal to 300/µL had a 70% (95% CI, 44-80) increased risk.^{7,8} In turn, this clearly emphasizes the importance of not taking FENO in isolation as a marker of type 2 inflammation, especially since eosinophils are predominantly driven by IL-5.

A strong recommendation was made for the role of FENO in monitoring disease activity and asthma outcomes where COE

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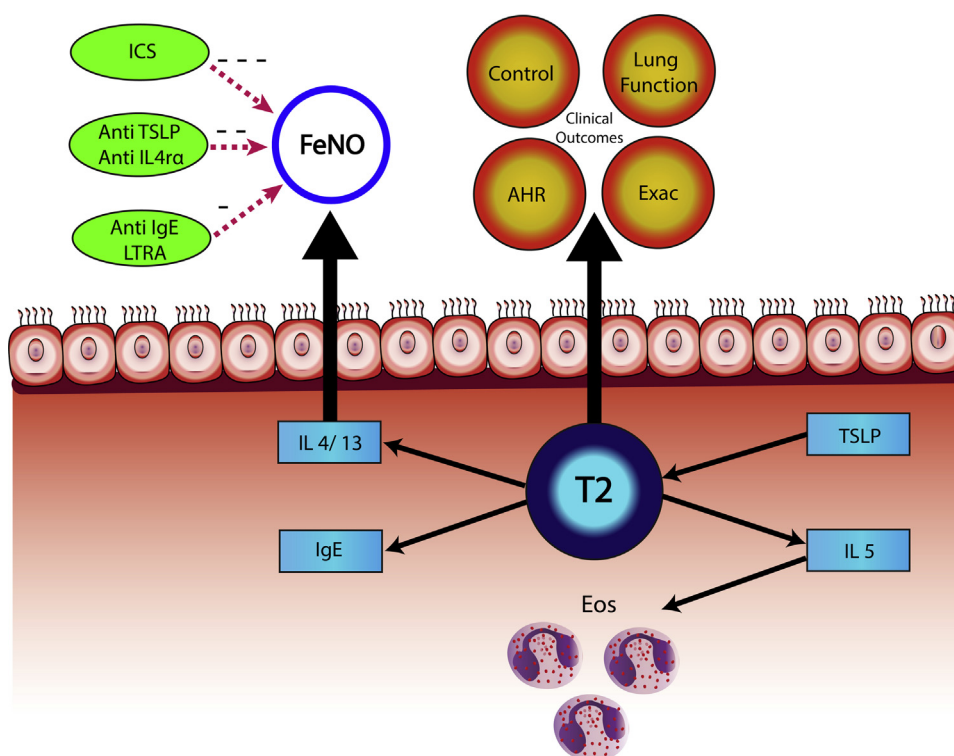


FIG 1. Schematic figure to portray the pivotal role of T2 inflammation in cytokine production, particularly IL-13–driven regulation of FeNO. Notably, FeNO has a relatively stronger association with exacerbations and AHR than with lung function or asthma control (as ACQ score or ACT score). ACT, Asthma Control Test; AHR, airway hyperresponsiveness; Eos, eosinophils; Exac, exacerbations; LTRA, leukotriene receptor antagonist; T2, type 2 inflammation; TSLP, thymic stromal lymphopoietin.

was low. In a primary care based trial, a baseline FeNO cutoff of greater than or equal to 40 ppb was associated with a 0.49 (95% CI, 0.14–0.84) reduction in the ACQ score when comparing response to low-dose ICS versus placebo.⁹ Moreover, a meta-analysis concluded that using FeNO to guide ICS dose adjustment resulted in an overall 42% (95% CI, 24–55) reduction in exacerbations.¹⁰ The Liberty Asthma Quest trial comparing dupilumab 200 mg versus placebo showed that a baseline FeNO of greater than or equal to 50 ppb was associated with a 69% (95% CI, 48 to 82) relative reduction in exacerbation risk compared with 25% (95% CI, –5 to 46) for FeNO less than 25 ppb, in keeping with its blocking effect on IL-4/13 signaling. For omalizumab in the *Study of Omalizumab (Xolair) in Subjects With Moderate to Severe Persistent Asthma (EXTRA)* study, comparing a baseline FeNO greater than or equal to 19.5 ppb versus less than 19.5 ppb was accompanied by a 37% greater reduction in exacerbations.

In terms of further research, we would especially like to see the development of a mobile application whereby clinicians could enter values for FeNO, blood eosinophils, past exacerbations, asthma control (ACQ or ACT), and FEV₁ to provide a prediction of future exacerbation risk (Fig 1).

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