What is the place of Fractionated Exhaled Nitric Oxide in the diagnosis and monitoring of pediatric asthma in 2023?

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Abstract

Fractional exhaled nitric oxide (FeNO) measurement is a partial and indirect estimate of eosinophilic bronchial inflammation. It can be performed in a reproducible, convenient and rapid manner from the age of 5 to 6 years. The FeNO measurement methodology has been validated by a European Respiratory Society / American Thoracic Society consensus. The American Thoracic Society, the National Institute for Health and Care Excellence and the European Respiratory Society have published recommendations with cut-off values for FeNO to guide the diagnosis, treatment and follow-up of asthma in children aged 5-16 years. Internationally validated percentile curves of FeNO values according to height, will allow us to interpret the FeNO value of the child and adolescent in a more statistically relevant way and to have a more accurate tool for diagnosis, phenotyping and follow-up.

Introduction

Nitric oxide (NO) is known as a pollutant but also as an important regulator in human asthma. Since 1987, we have known that NO is an endothelium-derived relaxing factor that regulates vascular and bronchial tone, promoting dilation. Airway inflammation has been recognised as an important physiopathological feature underlying asthma.

The presence and intensity of T-helper type 2 (Th2)-dependent bronchial pathology is a risk factor for wheezy infants to develop asthma in later life (1,2,3).

As symptoms and lung function measurements poorly reflect airway inflammation, a biomarker providing direct information on inflammatory processes could be of great interest for the diagnosis and management of asthma. It would allow early phenotyping and therefore appropriate treatment of asthma in young children, followed by convenient and regular monitoring.

Therefore, analysis of induced sputum eosinophils has been proposed to assess airway inflammation. In adults, treatment adjustments based on sputum eosinophils resulted in a reduction in the exacerbation rate (4). However, this technique requires expertise and is less suitable for children due to possible discomfort. A non-invasive approach is to measure fractional exhaled nitric oxide (FeNO) (5). The production of FeNO by inducible NO synthase in the lower airways is upregulated in the presence of T-helper type 2 cell inflammation and correlates with sputum eosinophil count (6,7).

Standardised methods for measuring FeNO were developed jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 1999 and revised in 2005 (8,9). The guidelines recommend the use of the term FeNO (fractional exhaled NO concentration) to describe the amount of NO in exhaled breath. FeNO is expressed in parts per billion (ppb), which is equivalent to nanolitres per litre. Further technical standards have been published by the ERS (10).

Most of the early studies reported in the literature used ozone chemiluminescence to measure FeNO concentrations and this technology was used in the first US Food and Drug Administration (FDA) approved devices (11). Chemiluminescence methods remain the gold standard and are more commonly used in research settings. Subsequently, more affordable devices based on other technologies (including handheld devices using electrochemical methods) have been approved for clinical use (10,12).

With these validated devices and following the ERS/ATS recommendations, the success rate of exhaled NO measurement increases from 40% at 4 years and 60% at 5 years to 100% at school age (8,9-12,14).

In this modest review of the literature, we will focus on four questions:

1. What factors influence FeNO levels?
2. Is FeNO measurement useful in the diagnosis of asthma?
3. What are the cut-off values for FeNO?
4. Is FeNO measurement useful for follow-up and further guidance of asthma management?

What factors influence FeNO levels?

Many factors independent of asthma influence FeNO levels (15).

Increase in FeNO

- Ethnicity: higher in blacks than in whites
- Age and height
- Sex: higher in males
- Allergic sensitisation
- Consumption of foods containing nitrite, caffeine and alcohol

Decrease in FeNO

- Smoke exposure (passive/active)
- Respiratory infection

Age

The relationship between FeNO level and the age of the child was highlighted by Buchvald et al. in 2005 in 405 children (14). In the population studied in this paper, the 95% upper limit varied from 15.7 ppb at 4 years of age, 28 ppb at 12 years of age, to 39.2 ppb at 14-17 years of age. Therefore, a single cut-off value of 35 ppb (NICE, ATS) or 25 ppb (ERS) for the diagnosis of asthma in all children is likely to create a problem of validity of interpretation.

Height

Wang et al in 2022 attempted to provide us with percentile curves of FeNO values as a function of patient size (Figure 1) using the UK data from non-asthmatic children in the population-based birth cohort Manchester Asthma and Allergy Study (MAAS) (15).

Obviously, these curves need to be validated before they can be used in routine clinical practice, and we will also need percentile type curves for the lower age groups from 4 to 5 years if possible.

Is FeNO measurement useful in the diagnosis of asthma?

The most widely recognised global consensus on asthma management is the Global Initiative for Asthma (GINA), the latest report of which was published in 2022 (16). This consensus does not differentiate between adults and children for the diagnosis of asthma.

The European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years, published in the European Respiratory Journal in 2021, propose an algorithm for the diagnosis of paediatric asthma based on clinical data, spirometry, challenge testing, FeNo and, if necessary, bronchial challenge testing (17).

What are the cut-off values for FeNO? (Figure 2)

Many clinical guidelines use FeNO as a dichotomous outcome ('positive' or 'negative') to facilitate the diagnosis of asthma in children. However, the cut-off values are not consistent between guidelines. In the NICE guidelines, the paediatric threshold for a diagnosis of asthma is 35 ppb at 50 ml/sec, whereas in the European Respiratory Society (ERS) guidelines it is 25 ppb (17,18). Furthermore, there is a significant overlap in FeNO levels between healthy and asthmatic populations and the range is wide (19).

In 2011, the ATS made suggestions for interpreting FeNO levels in asthma (16):

-A FeNO less than 25 ppb in children aged >12 years and less than 20 ppb in children younger than 12 years suggests noneosinophilic airway inflammation or the absence of airway inflammation and a low likelihood of response to inhaled corticosteroid therapy.

-FeNO greater than 50 ppb in children > 12 years of age or greater than 35 ppb in children < 12 years of age indicates eosinophilic airway inflammation and a high likelihood of response to inhaled corticosteroid therapy.

-Values of FeNO between 25 and 50 ppb in children > 12 years and 20 to 35 ppb in children < 12 years should be interpreted cautiously with reference to the clinical situation.

-An increase in FeNO of more than 20 per cent and more than 25 ppb (20 ppb in children under 12 years) from a previously stable level suggests increasing eosinophilic airway inflammation, but there is wide inter-individual variation.

-A decrease in FeNO of more than 20 per cent for levels above 50 ppb or more than 10 ppb for levels below 50 ppb may be clinically important.

Figure 1: Proposed FeNO percentile chart from MAAS cohort (reproduced from: Wang R et al. ERJ Open Research 2022;8:00319-2022 (15).

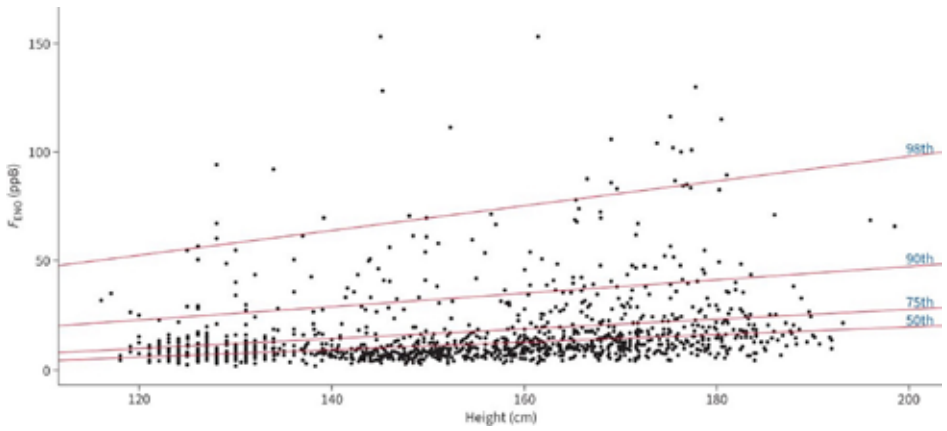

Figure 2: Cut-off values, according age, asthma endotype, mentioned in different guidelines: ATS, ERS, NICE, MAAS cohort, Ran Wang.

In symptomatic patients <6 weeks (cought or dyspnea or wheezing)	ATS	ERS	NICE U-K	Maes cohort Ran wang	
In favor of a diagnosis of childhood asthma		25 ppb	35 ppp	>perc 90	> perc98
Ages		*5-16 years	*5-16 years	110-200 cm	110-200 cm
In favor of symptomatic eosinophilic airway inflammation	35ppb			sens 58,8	sens 33,3
and high probability of response to inhaled corticotherapy	< 12 years			spec 95,5	spec 100
Ages	50 ppb			PPV 96,8	PPV 100
	> 12 years			NPV 50	NPV 39,3
Noneosinophilic airway inflammation or the absence of airway	<20 ppb				
inflammation and low probability of response to inhaled corticotherapy	<12 years				
	<25 ppb				
	> 12 years				

Figure 3: Asthma risk stratification based on percentile cut-off (reproduced from: Wang R et al. ERJ Open Research 2022;8:00319-2022 (15).

TABLE 5 Asthma risk stratification based on percentile cut-off.

Percentile	Sensitivity, % (n)	Specificity, % (n)	PPV, % (n)	NPV, % (n)	+LR#	−LR¶
>50th	78.4 (40/51)	40.9 (9/22)	75.5 (40/53)	45.0 (9/20)	1.3	0.5
>75th	72.5 (37/51)	77.3 (17/22)	88.1 (37/42)	54.8 (17/31)	3.2	0.4
>90th	58.8 (30/51)	95.5 (21/22)	96.8 (30/31)	50.0 (21/42)	13.1	0.4
>98th	33.3 (17/51)	100 (22/22)	100 (17/17)	39.3 (22/56)	∞	0.7

#: +LR: sensitivity/(1-specificity). ¶: −LR: (1-sensitivity)/specificity. LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

While a single diagnostic cut-off may be easy for clinicians to implement in practice, it is clear that the clinical probability of asthma increases with increasing FeNO levels above the recommended cut-off, and reducing this continuous variable to a dichotomous outcome loses an important amount of information (17,19,20).

As mentioned above, pubertal growth spurts influence the trajectory of FeNO, potentially further compromising diagnostic accuracy within this age group when using a single fixed cut-off (21).

The measurement of FeNO using the percentile curves of Wang et al. allows to optimise the rigorous diagnosis of asthma with a simple, not very invasive and inexpensive test. We can see that from the 90th percentile, the specificity of the diagnosis of paediatric asthma increases to more than 95%, with a PPV of 97% for a sensitivity of almost 59% and a NPN of 50% (15).

On the other hand, we know that a patient with another atopic condition, e.g. allergic rhinitis, without the slightest asthma symptom may have an exhaled FeNO at the 90th percentile or above without having asthma by definition.

Therefore

-An exhaled NO test should not be performed in a patient who does not have symptoms suggestive of asthma that are recurrent or have been present for at least 6 weeks.

-The FeNO value should be interpreted according to an algorithm that takes into account the clinical context, baseline spirometry and bronchodilator challenge, if available.

-In inhaled corticosteroid (ICS) naïve patients with chronic symptoms (more than 6 weeks) or recurrent symptoms partially suggestive of asthma (cough, isolated exertional dyspnoea, ...), even in the absence of reversible obstruction on classic spirometry, a value ≥ 35 ppb for NICE recommendations, ≥25 ppb for ERS recommendations, > 90th percentile on Wang's percentile curve, favours the diagnosis of paediatric asthma (Figure 3).

-The value of FeNo > 90th percentile according to Wang et al. could be of great clinical interest after validation, as it is very specific with a high PPV in patients with asthma symptoms.

Is FeNO measurement useful for follow up and further guidance of asthma management?

Asthma exacerbations contribute significantly to asthma mortality and healthcare costs. It is an important prognostic factor in paediatric asthma according to the long-term goals for asthma management in the Global Initiative for Asthma 2022 (16).

In 2014, our Belgian multi-centre, single-blind, randomised controlled trial of ninety-nine children with persistent allergic asthma concluded that FeNO measurements in childhood asthma management did not improve the proportion of symptom-free days, but resulted in fewer asthma exacerbations associated with increased leukotriene receptor antagonist use and increased inhaled corticosteroid doses (22). Our aim was to keep FeNO below 20 ppb, the rounded 95% upper limit of FeNO levels in healthy children derived from previous studies.

Are these conclusions still valid in 2023?

For the follow-up of asthma, GINA 2022 makes a clear distinction between adults and children: "In children and young adults with asthma, FeNO-guided treatment was associated with a significant reduction in the number of patients with ≥ 1 exacerbation (OR 0.67) and in the exacerbation rate (mean difference -0.27 per year) compared with guideline-based treatment (evidence A); similar differences were seen in comparisons between FeNO-guided treatment and non-guideline-based algorithms (16).

The most recent meta-analysis on this topic was published by Xia Wang et al. in 2022 and selected 23 randomised controlled trials (from 2005 to 2020 with 2723 paediatric asthma patients, 1360 in the intervention group vs. 1363 in the control group) comparing the effects of FeNO-guided asthma management with those not using FeNO in paediatric asthma (23).

According to this meta-analysis: "FeNO-guided asthma management helped to reduce the number of children with asthma exacerbations (risk ratio (RR) 0.73, P < 0.0001) and the frequency of exacerbations (standardised mean difference (SMD) -1.57; P < 0.00001).

We can conclude that, although there is still no consensus on the treatment algorithm guided by the measurement of exhaled NO, the FeNO-guided asthma management strategy could partially improve the outcome of paediatric asthma by reducing the risk of exacerbation, which is an essential prognostic factor in paediatric asthma according to the long-term goals of asthma management (GINA 2022), and by increasing inhaled corticosteroid therapy (16).

Currently, in practice, for follow-up and therapeutic adaptation, we could propose to fully respect the recommendations of the ATS interpretation rules.

The following guidelines can be suggested:

- if an asthmatic patient remains symptomatic for more than 1-3 months despite background treatment with:
  - either an exhaled NO level > 20 ppb (or > perc 75 according to R. Wang) and even more if > 35 ppb (or > perc 90 according to R. Wang) or if the follow-up exhaled NO level increases significantly +20% (baseline >50 ppb) or +10ppb (baseline < 50 ppb).
  - An increase in ICS dose or compliance or improvement in allergen avoidance has a high likelihood of improving asthma control.
  - Corticoresistance cannot be excluded.
  - Without an increase in ICS dose, there is a high risk of exacerbation (if > 35 ppb or > PERC 90 according to R. Wang).
  - Either an exhaled NO value <20 ppb (or < perc 75 according to R. Wang) or if the follow-up exhaled NO value has significantly decreased by -20% (baseline >50 ppb) or -10ppb (baseline <50 ppb).
  - Symptoms are unlikely to be due to eosinophilic airway inflammation.
  - Increasing ICS dose or compliance is unlikely to improve asthma control.
  - Questions to ask about diagnosis, comorbidities, passive smoking...
- When an asthma patient has been asymptomatic for at least 3 months on the same background treatment:
  - either an exhaled NO value > 20 ppb (or > perc 75 according to R. Wang) and even more if > 35 ppb (or > perc 90 according to R. Wang) or if the follow-up exhaled NO value increases significantly by +20% (baseline >50 ppb) or +10ppb (baseline < 50 ppb).
  - Reducing the dose of ICS is likely to reduce asthma control and should be done very gradually and cautiously.
  - Either an exhaled NO level <20 ppb (or < Perc 75 according to R. Wang).
  - A decrease in ICS dose has a low risk of decreasing asthma control and could be achieved quickly.

Conclusions

Measurement of exhaled NO is simple, fast and reproducible from the age of 5-6 years. The technique is not reimbursed in Belgium. The

measurement modalities in children are well specified by the ERS and ATS consensus.

Even if this is not the case for adults, sometimes smokers and carriers of polypathology, we can consider that, in the paediatric field, the measurement of exhaled NO is useful for the diagnosis of eosinophilic asthma in non-smoking patients, without inhaled corticosteroids, with asthma-like symptoms for at least 6 weeks. This measurement must always be interpreted in conjunction with clinical data and, if possible, the results of spirometry with bronchodilator challenge. The interest of this measurement lies in its strong positive predictive value and high specificity, although a normal value cannot exclude the diagnosis of asthma.

Even if this is not the case in adult patients, FeNO data can improve the management of the background treatment of asthma in children. It could lead to a reduction in the number of exacerbations and avoid inappropriate dosing of inhaled corticosteroid therapy.

The use of size-based percentile curves, or even in the future the use of z-score statistical tools, may allow a more statistically valid analysis of exhaled NO levels and a clearer and more rigorous follow-up.

Pending the validation of these curves, the fixed cut-off values proposed by the ATS and NICE recommendations can be used, i.e. FeNO < 20 ppb at 50 ml/sec, corresponding to a low probability of bronchial eosinophilic inflammation and therefore a low probability of efficacy of inhaled corticosteroid therapy, whereas a value > 20 ppb and even more > 35 ppb corresponds to a higher probability of bronchial eosinophilic inflammation and therefore a higher probability of efficacy of inhaled corticosteroid therapy (8,18).

Thus, a FeNO level of ≥ 35 ppb or ≥25 in a paediatric patient who has been symptomatic for more than 6 weeks without inhaled corticosteroid therapy makes the diagnosis of asthma more likely, but a normal FeNO level cannot exclude the diagnosis of asthma.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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