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Fractional exhaled Nitric Oxide monitoring in paediatric asthma management

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Clinical Questions:

Does monitoring of childhood asthma using fractional exhaled nitric oxide (FeNO):

a. reduce asthma exacerbations
b. reduce steroid prescriptions
c. improve asthma-related quality of life

Background, Current practice and Advantages over Existing Technology:

Current recommendations are that children with asthma should be reviewed 6 monthly at minimum according to The National Heart, Lung and Blood Institute (NHLBI) guidelines in America (1), or annually according to The Scottish Intercollegiate Guideline Network (SIGN) (2) and the National Institute for Health and Care Excellence (NICE) (3) in the UK. NICE and SIGN suggest this review should include an assessment of control by monitoring the severity and frequency of exacerbations, inhaler adherence and technique plus a symptom score, such as the Children's Asthma Control Test (C-ACT) or the Asthma Control Questionnaire (ACQ) (1,2). The positive predictive value of symptom scores for asthma exacerbations depends on the cut-off used, but was reported to be 46.7% for the C-ACT at the recommended score of <24/27. This increased to 100% at the lower value of <19/27 with a corresponding lower sensitivity (4). The results suggest that using the current symptom scores alone could result in significant numbers of children being overtreated with associated risks from excess or unnecessary treatment. Potential additional measures of control are sometimes used in primary care, such as routine testing of Peak Expiratory Flow or spirometry, but these have not been shown to reduce symptom scores or improve quality of life compared to symptom-based management alone (5) and an association between forced expiratory volume (FEV1) and asthma attacks is debated with inconsistent results across studies (6). There is therefore a need to better identify those children with insufficient disease control and therefore at risk of exacerbations and add additional objective measures of control, with FeNO one possible solution.

FeNO has the potential to provide additional clinical information, such as quantifying the degree of eosinophilic airway inflammation (8). This information could help to identify which patients are most likely to benefit from an adjustment in their inhaled corticosteroid (ICS) regimen as opposed to other treatment options. Whilst tests such as Peak Flow measures and spirometry can be difficult for young children to complete, FeNO has been shown to be reproducible and feasible in children aged 4 or older (9). Child friendly versions are available, linked to computer software to encourage children to use the technology in the correct manner and improve reliability. Newer FeNO monitors tend to be hand held devices, offering portable, point-of-testing to provide flexibility and speed of diagnosis.

Details of Technology:

Inflammation causes eosinophils in the lungs to produce nitric oxide, which is then released in exhaled breath. It reacts with atmospheric trioxygen in a chemiluminescence reaction to become nitrogen dioxide, emitting light as it transitions from an excited to a ground state. This emitted light is proportional to the amount of exhaled nitric oxide, which reflects the amount of underlying lung inflammation and is the basis for the clinical application. Three separate devices to measure this exhaled nitric oxide have been evaluated by NICE and are the most widely used: NObreath, NIOX VERO and NIOX MINO.

NIOX MINO is a hand-held portable device manufactured by Aerocrine that uses an electrochemical sensor to analyse the concentration of exhaled nitric oxide. It requires a ten second exhalation with the last 3 seconds of exhaled breath being analysed. It is accurate to +/-5ppb and precise to <3ppb of measured value <30ppb or <10% of measured value ≥30ppb (10,11). NIOX MINO has been validated for both school-age children and adults. In pre-school children where co-ordinated or prolonged exhalation is difficult, offline exhaled breath has been collected in bags and measured, though this is not its recommended use. The machine can self-calibrate, although Aerocrine recommend the sensor is changed yearly. NIOX MINO must be plugged into a power outlet and has a minimum instrument 'shelf-life' of 3 years. It costs £2,468 (all quoted prices inclusive of VAT) and an additional £4.93 - £9.35 per test for the sensor and filter, depending on the quantity bought (12). Aerocrine's upgrade on the NIOX MINO, the NIOX VERO, comes with a rechargeable battery pack that charges in under 8 hours and will last for up to 30 measurements per charge with a battery life of around one year and a guaranteed device operational life of 5 years (12). The NIOX VERO costs £2,540 for the instrument and an additional £4.62 - £8.75 per test. Previous NIOX systems have also been used in some studies, such as NIOX FLEX, which used similar technology but was a desktop computer based system. These have now largely been replaced by the cheaper, more accurate versions above and are therefore not included in NICE guidelines.

NObreath is the Bedfont Scientific equivalent and is also a hand-held, battery powered device. It requires a 12 second breath exhalation in adults and 10 seconds in children, is sensitive to +/- 5ppb, works between temperatures of 10-30°C and takes under a minute to warm up to use. It costs £1,794.00 (13) with similar additional costs to NIOX MINO for test equipment.

There are other desktop-based models on the market but these have not been included in the current NICE guidelines. Although the reason for this is not stated, NICE seem to have focused on the most studied models and excluded some of the older or less portable devices. Ecomedics have an Analyser CLD 88 sp model that is a computer desktop based system, with options of single or multiple breath options to aid use when patients are unable to co-ordinate their breathing as required. Yearly service and maintenance is recommended. General Electric Company manufacture the desktop Sievers Nitric Oxide Analyser (NOA 280i), which offers a range of NO collection devices, including nasal sampling and offline bag collection of exhaled breath for later analysis. It is accurate to +/-5ppb and requires servicing every 6 months.

Patient Group and Use:

- Reducing children's risk of future asthma exacerbations by optimisation of steroid dosing
- Helping guide physicians in deciding between increasing steroid dose versus addition of long acting bronchodilator at Step 3 of asthma treatment ladder.

Importance:

An estimated 300 million people worldwide have asthma and up to 250,000 die prematurely each year, as many as 90% of which are thought to be avoidable (14). In the UK 1 in 11 children have asthma (15), in the USA 14% of children are diagnosed with asthma and in Western Europe 6.2% of 13-14 year-olds reported

severe asthma in a 12 month period (16,17). Asthma is directly linked to 4.1 million GP consultations and over 25,000 paediatric hospital admissions per year in the UK, costing the NHS over £1 billion per year. The National Review of Asthma Deaths (NRAD) 2014 found that 57% of those who died from asthma were under primary care supervision only and in 46% of the deaths in the study period, factors were identified in terms of implementation of asthma guidelines that could have made death less likely (18). Of those who died where prescription data was available, 39% (65/165) had been prescribed over 12 short-acting reliever inhalers in the previous year and 4% (6/165) over 50, reflecting a pattern of excessive use of reliever medication. Conversely preventer medication appeared under-prescribed with 80% not collecting the recommended 12 preventer inhalers per year and 38% using under 4 preventer inhalers in a 12 month period (18). Clinicians need to improve their assessment of future asthma risk and tend to over-focus on current quality of life, reflected in these prescribing patterns. Equally those on regular ICS should be reviewed and appropriately stepped down when well controlled, given the risks of excessive steroid use in asthma, including increased risk of lower respiratory tract infections (19). Finding more reliable ways of monitoring asthma could therefore improve control to reduce both morbidity and mortality as well as reduce the number of children being over treated.

Previous Research:

Impact compared to existing technology

Characteristics of included studies

Table 1 summarises the study characteristics of the nine RCTs we identified that assessed the relationship between FeNO monitoring in asthmatic children and their asthma control. The study outcomes included the number of acute asthma exacerbations, changes in dosage of inhaled corticosteroids and asthma-related quality of life. All nine RCTs were conducted in secondary care, predominantly in Western Europe, enrolled patients with a range of asthma severities and used sample sizes ranging from 47 to 546 participants. Aerocrine manufactured NIOX equipment was used in seven studies (20-26). Six studies involved run-in periods ranging from 2 to 16 weeks to stabilise treatment before randomisation (20-22, 25-27). In six studies children were specifically recruited with a history of allergic asthma, usually confirmed as RAST 2 positive to at least one airborne allergen and in some cases with additional positive IgE or skin prick test (20-21,23-24,26-28). In two of the three studies where participants were not allergy tested there was a significantly increased use of ICS in the FeNO groups by the end of the study, although neither study found any related improvement in quality of life or significant reduction in exacerbations (25,27).

Asthma exacerbations were defined in a variety of ways, with most studies using hospital admission, unplanned review or need for oral steroids (20-23, 26). All except one study (26) used a local guideline-based symptom score as their comparator and most included symptom control scores into their treatment algorithm (21-26). Most studies have taken a pragmatic approach and added FeNO to standard care so that in all but two studies a step down in treatment would not be done when the FeNO alone was low if symptoms remained uncontrolled (21-27). In one study treatment would actually still be increased in the intervention arm irrespective of the FeNO result if control was deemed to be poor (26).

Table 1 - Randomised Controlled Trials (RCTs) using FeNO in paediatric asthma management

Author	Population	Setting	Intervention	Comparator	FeNO threshold to increase treatment	FeNO threshold to decrease treatment	FeNO device
Voorend-van Bergen et al. 2015 (20)	n=272 age- 4-18 persistent asthma †	5 General Paediatric clinics and 2 tertiary referral centres in the Netherlands	Intervention arms; 1.Web-reported ACT, 2. ACT and FENO	Standard care including ACT	≥50ppb	≤25ppb	NIOX MINO or NIOX chemi-lumines-cence analyser
Pijnenburg et al. 2005 (21)	n=85 age- 6-18 moderate to severe asthma †	Paediatric Pulmonology outpatient clinic in the Netherlands	Symptoms + FeNO	Symptom based treatment	≥30pbb	<30ppb - unless symptoms poorly controlled	NIOX 'analys-er' - model not stated
Pike et al. 2013 (22)	n=90 age- 6-17 moderate to severe asthma	Paediatric outpatient clinics at four hospitals in the UK	Algorithm ap-proach combin-ing FeNO and asthma contro.	Symptom con-trol based on SIGN and BTS guidelines.	≥25ppb or double in FeNO - ICS increase ≤25ppb and poor symptom control - LABA increase.	≤15ppb - unless symptoms poorly controlled.	NIOX MINO
De Jongste et al. 2008 (23)	n=151 age- 6-18 stable, mild to moderate asthma †	5 academic centres and 12 hospital outpa-tient clinics in the Nether-lands	Daily symptom scores + FeNO	Daily symptom score recorded in a palmtop electronic diary	≥20ppb for chil-dren aged 6-10 years ≥25ppb for chil-dren older than 10 years	If below these thresholds and symptoms con-trolled then step-down	NIOX MINO
Peirsman et al. 2013 (24)	n=99 age- 5-14 mild to severe asthma †	Paediatric outpatient clinics at 7 Belgian hospi-tals	GINA guideline plus FeNO score	Standard care based on GINA guidelines	≥20ppb	<20ppb - unless symptoms poorly controlled.	NIOX MINO
Szefler et al. 2008 (25)	n=546 age-12-20 uncontrolled asthma (57% moderate to severe)	12 hospital outpatient clinics USA	NAEPP guide-lines + FeNO	NAEPP guide-lines alone	Step-up if ≥ 20ppb and adherence ≥50% on 2 con-secutive visits	<20ppb and 're-duction in symp-toms'	NIOX system, rapid-response analyser - model not stated
Fritsch et al. 2006 (26)	n=47, age- 6-18 mild to mod-erate asthma †	Paediatric Pulmonology Hospital out-patient clinic, Austria	Index + FeNO Step-up irre-spective of FeNO if patients met criteria for poor control as per control group.	Symptoms, B-agonist use and lung function.	≥20ppb. Also step-up if FEV1<80% predicted, mild symptoms in past 4/52 or b-agonist use ≥6puffs/14 days.	All other cases step-down	NIOX 'instru-ment' - model not stated

Author	Population	Setting	Intervention	Comparator	FeNO threshold to increase treatment	FeNO threshold to decrease treatment	FeNO device
Petsky et al. 2015 (27)	n=65 age- 4-18 with persistent asthma	Paediatric outpatient dual-centre study between Brisbane and Hong Kong	Management based on FeNO levels alone	Standard care based on Australian National Asthma Council and GINA guidelines	≥10 ppb with negative skin prick test ≥12ppb with 1 positive SPT ≥ 20ppb with 2 or more positive SPT	Step-down in treatment if below the same thresholds	Sievers NOA 280i chemiluminescence analyser.
Verini et al. 2010 (28)	n=64, age- 6-17 predominantly mild to moderate asthma †	Paediatric Pulmonology and Allergy Hospital Outpatient Clinic, Italy	GINA guidelines + FeNO score	GINA guideline based treatment	≥12ppb	<12ppb	Ecomedics CLD 88 chemiluminescence assay.

† - patients recruited with allergic asthma. All age ranges are in years.
Abbreviations in table- ACT- Asthma Control Test, FeNO - Fraction Exhaled Nitric Oxide, ppb - parts per billion, SIGN - Scottish Intercollegiate Guideline Network, ICS - inhaled corticosteroids, LABA - long acting beta agonist, GINA - Global Initiative for Asthma, NAEPP - National Asthma Education and Prevention Programme, FEV1 - forced expiratory volume in 1st second, SPT - skin prick test

Outcome measures

1. **Impact on number of asthma exacerbations**

Two studies reported that FeNO-guided management was associated with fewer participants experiencing one or more exacerbations of asthma (24,27). However, only one of these studies also reported a significantly lower rate of exacerbations among participants in the FeNO group (24). This study (24) defined exacerbations based on symptom criteria stated by GINA guidelines, whereas the other (27) defined exacerbations as episodes requiring prescription of oral steroids, with or without hospital admission.

One study did not observe a significant difference between FeNO and non FeNO groups in the proportion of participants who had one or more exacerbation, but did report that fewer children in the FeNO group were prescribed one or more courses of oral steroids (32.1%, 95% CI 25.3% to 36.7%) than in the comparator group (42.0% 95% CI 35.1% to 47.4%; mean difference -10.3, 95% CI -18.5 % to -2.2%, p=0.0137) (25). In another study, 8 courses of oral prednisolone were prescribed in 7/42 participants who received FeNO-guided management, compared to 18 courses of oral prednisolone prescribed to 10/47 participants who received symptom-guided management (21). However, this difference was not statistically significant (p=0.60), possibly because six children in the group who received symptom-guided management were prescribed multiple courses of prednisolone, compared to only one child in the FeNO group.

The remaining study which collected data on asthma exacerbations reported a longitudinal reduction in mean exacerbation frequency from baseline after six months and 12 months, but did not perform any formal comparisons between the FeNO- and guideline-based management groups at either follow-up stage (28).

Table 2 - Summary of results from studies which assessed the effectiveness of FeNO-guided asthma monitoring on reducing asthma exacerbations.

Study	Definition of exacerbation	Main findings
Petsky et al. 2015 (27)	1. Prescription of oral steroids, with or without hospital admission	A significantly lower proportion of children in the FeNO group had ≥1 exacerbation over the 12-month study period (6/31 FeNO versus 15/32 control, p=0.017). However, the rate of exacerbations in the FeNO group (0.39 per person-year) was not significantly lower than that in the control group (0.78 per person-year, p=0.102).
Pijnenburg et al. 2005 (21)	1. Prescription of oral steroids or hospital admission.	Based on prescription of oral steroids, eight exacerbations occurred in the FeNO group compared to 18 in the group who received symptom guided management. However, the difference between groups was not statistically significant (p=0.60). One participant randomised to FeNO-guided management, was hospitalised due to a severe asthma exacerbation.
Szefler et al. 2008 (25)	Any one or more of: 1. Prescription of oral steroids 2. Hospital admission 3. Unscheduled visits	Fewer children were prescribed ≥1 courses of oral steroids in the FeNO group (32.1%, 95% CI 25.3% to 36.7%) than in the comparator group (42.0% 95% CI 35.1% to 47.4%; mean difference -10.3, 95% CI -18.5 % to -2.2%, p=0.0137). However, no significant difference was shown between the two groups in terms of the proportion of children who had ≥1 exacerbation (mean difference -6.5% 95% CI (-14.4% to 1.4%, p=0.1068).
Peirsman et al. 2013(24)	1. Episode of progressive increase in shortness of breath, cough, wheeze or chest tightness, or a combination of these symptoms as stated by GINA guidelines.	A lower number of asthma exacerbations was observed over 12 months in the FeNO group (18 exacerbations) than in the comparator group (35 exacerbations, p=0.02). The proportion of children who had ≥1 exacerbation was also significantly lower in the FeNO group (11/46, 23.9%) than in the comparator group (22/46, 47.8%; p=0.02).
Verini et al. 2010 (28)	1. Episode of cough, dyspnoea, and wheeze as per ATS-ERS criteria, requiring short-acting β2-adrenergic agonist.	Significant longitudinal reductions in mean exacerbation frequency from baseline were observed after 6 months and 12 months in the FeNO group (baseline 1.96 ± 1.18; 6 months 1.01 ± 0.96, p=0.0003; 12 months 0.83 ± 0.98, p=0.0001). However, no comparisons between the FeNO and non FeNO groups were made at either follow-up stage.

Abbreviations in table- FeNO = fractional exhaled nitric oxide, CI = Confidence Interval, GINA = Global Initiative for Asthma , ATS-ERS= American Thoracic Society and European Respiratory Society

2. **Impact on inhaled corticosteroid prescriptions**

Four studies reported a significantly higher final ICS dose in the FeNO group of between 100mcg to 200mcg above that in the comparator (24-27). Three of these four studies showed a reduction in exacerbations, suggesting appropriately targeted ICS use will have a therapeutic effect (24,26-27). Two studies saw a similar decrease in ICS dose in both intervention and comparator arms (20,23) and two showed no change in dose in either arm (21-22). In all four of these studies there was no significant change in exacerbation frequency or measures of asthma control. One study showed no change in dose in the FeNO arm, but an increase in ICS in the comparator arm, though there was a reduction in the incidence of exacerbations in the FeNO arm whilst not in the comparator arm (28).

There was a wide variation in the FeNO threshold to step-up treatment, ranging from 10ppb to 50ppb and an association between this threshold value and the subsequent ICS dose. Four of the five studies with a lower threshold of ≥20ppb to step-up treatment saw an increase in ICS dose in the FeNO group (24-27). The

four studies with the highest FeNO threshold (≥25ppb for step-up) all saw either a reduction or no change in ICS dose and no change in outcomes between the FeNO group and the control (20-23).

3. **Impact on asthma-related quality of life**

Four studies used either the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) or the Paediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ) (20,22-23,27), with two using both (20,27). There was no significant difference in any of these results between the FeNO and comparator groups on asthma-related quality of life.

4. **Impact on cost effectiveness**

An economic evaluation was conducted alongside a randomised control multi-centre trail to assess cost-effectiveness of 4-monthly monitoring using FeNO, compared with web-based monthly monitoring and standard care in children with asthma in Netherlands (29). The trail had a 1 year follow up and the sample size was 272. Patients' health related quality of life was measured using the EQ-5D-3L and Quality Adjusted Life Years (QALYs) were calculated using the area under curve method based on the Dutch tariff of EQ-5D. Costs were assessed from both health care and societal perspectives using a cost questionnaire. No statistically significant differences were found in QALYs and costs between FeNO, web-based monitoring and standard care. From a health care perspective, the FeNO-based strategy was 20% likely to be the most cost effective at a willingness to pay threshold of €40,000 per QALY compared to the other two. On the other hand, from a societal perspective, the FeNO-bases strategy was favoured over a wide range of willingness-to-pay values and had the highest chance (83%) of being most cost-effective at a willingness to pay of about €40 000/QALY. This study showed that FeNO-based strategy could potentially be a cost effective way to monitor children's asthma especially compared with standard care.

Accuracy compared to existing technology

Only the Szefler et al. study documents both the percentage of well controlled patients and their FeNO scores (25). They reported that 57.3% (306/534) were well controlled for 80% or more of the study period but despite this only 35.6% of participants had FeNO levels <20 ppb on 80% or more of their visits (25), again raising the issue of the best FeNO threshold for treatment adjustment, but also whether the current measures of control are accurately detecting those who are sub-optimally controlled. Few studies have correlated their findings with other potential markers of airway inflammation but where they do, there is some evidence to show that there is a corresponding reduction in IL-5 with a reduced FeNO (30), although this was not always replicated in other studies (31).

In one study where re-calibration of the FeNO device was done after the studies were complete, there was evidence of 'drift outside the manufacturer's specification', but this was not significant enough to alter the subsequent treatment decision (23). The reproducibility of the FeNO scores have not been documented in these studies, however the ease of use of the machines means that the test can be easily repeated at point of testing to improve reliability by taking a consistent plateau NO measurement (26). Although rarely commented on, the extremely low drop-out rate across the studies suggest that the FeNO measurement has good acceptability.

Guidelines and recommendations

The latest NICE guidelines have recommended the use of FeNO alongside other investigations to help correctly identify asthma when there is diagnostic uncertainty (32,33). NICE also suggest it should be used where patients remain symptomatic despite ICS to help guide treatment decisions (33). They recommend a cut-off of 19-21ppb based on previous studies, but recognise that sensitivities have been quoted from between 49% and 86% for this range. NICE have yet to recommend FeNO should be used for routine monitoring of asthma in children as there is currently insufficient evidence to support this. The American Thoracic Society suggest that FeNO may have benefits over more established tests such as FEV1 reversibility in iden-

tifying eosinophilic airway inflammation and those likely to benefit from ICS, monitoring therapeutic response to ICS, and helping identify non-adherence to ICS treatment (34). SIGN guidelines recognise there is some evidence to suggest FeNO may help guide ICS use, but recommend the evidence is not robust enough to support routine use at this stage and suggests further research is required (2).

Research Questions:

1. What is the optimal FeNO level cut off to use for step-up and step-down in treatment?
2. What other factors can influence measured FeNO levels?
3. How can FeNO be incorporated into monitoring strategies to improve asthma control?
4. Is measurement of FeNO in primary care a cost-effective addition to current management?

Suggested next steps:

Further investigation to establish FeNO thresholds for treatment change, with consideration whether this should be age and device dependent.
High quality RCT study set in primary care setting to assess impact of FeNO use on asthma control, exacerbations, ICS use and quality of life.

Expected outcomes:

At present there is a lack of adequately powered and well-designed studies showing a benefit from FeNO measurement to support its routine use in primary care for asthma monitoring in children. However, if the optimal decision thresholds and role of FeNO in asthma monitoring could be established, its ease of use, portability and reproducibility would make it a potentially important tool for guiding treatment in primary care. The RCTs here suggest it has the potential to reduce asthma exacerbations by appropriate targeting of increased ICS dose. Long-term, a targeted strategy for asthma treatment with adequate doses of ICS and a subsequent reduction in exacerbations may be cost-effective due to reduced costs of hospitalisation and serious complications.

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