Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial

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AUTHORS CONTRIBUTIONS

The study was conceived by GR and developed with the other authors. KP, NL, KD, RM, AS and SP assessed the study participants. KP and GR analysed the study data and prepared the first draft of the manuscript. All the authors reviewed and discussed the data and approved the final manuscript.

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ABSTRACT

Introduction

Inhaled corticosteroid therapy (ICS) for asthma is currently modified according to symptoms and lung function. Fractional exhaled nitric oxide (FENO) has been demonstrated to be a non-invasive marker of eosinophilic inflammation. Studies of FENO-driven asthma management show variable success.

Objectives

This study aimed to evaluate whether monitoring FENO can improve outpatient management of children with moderate to severe asthma using a pragmatic design.

Methods

Children aged 6-17 years with moderate to severe asthma were recruited. Their asthma was stabilised before randomisation to FENO-driven therapy or to a standard management group where therapy was driven by conventional markers of asthma control. ICS or long-acting bronchodilator therapies were altered according to FENO levels in combination with reported symptoms in the FENO group. Participants were assessed 2-monthly for 12 months. ICS dose and exacerbation frequency change were compared between groups in an intention to treat analysis.

Results

Ninety children were randomised. No difference was found between the two groups in either change in corticosteroid dose or exacerbation frequency. Results were similar in a planned secondary analysis of atopic asthmatics.

Conclusion

FENO-guided ICS titration does not appear to reduce corticosteroid usage or exacerbation frequency in paediatric outpatients with moderate to severe asthma. This may reflect

limitations in FENO-driven management algorithms, as there are now concerns that FENO levels relate to atopy as much as they relate to asthma control.

Trial registration: Controlled-Trials ISRCTN50872816.

Keywords: asthma, exhaled airway markers, paediatric, therapy

The trial was approved by Southampton and South West Hampshire Research Ethics Committee (06/Q1702/9) and registered with Controlled-Trials.Com (ISRCTN50872816). Informed consent was obtained from each child's parents.

INTRODUCTION

Asthma is a disease of airway inflammation [1]. Sputum eosinophil count-guided management has been shown to reduce exacerbation frequency in adult patients without increasing inhaled corticosteroid dose [2]. However, sputum induction can be difficult in young children [3]. Inhaled corticosteroid therapy (ICS) in asthmatic children is currently modified according to symptoms and lung function, both of which poorly reflect airway inflammation [4] and poorly predict exacerbations [5]. A suitable clinical measure of airway inflammation might enable optimisation of individual patients' ICS dose.

Fractional exhaled nitric oxide (FENO) has been proposed as a non-invasive measure of eosinophilic inflammation which can be measured in children [6] and may be a marker of asthma control. [7-10] Asthmatic subjects have higher mean FENO concentrations than non-asthmatic controls [11] and FENO has been shown to increase with worsening asthma control [6] and with allergen exposure in children with grass pollen-induced asthma [9] Inhaled corticosteroids have been shown to reduce FENO in children with asthma [12]. Together

these observations suggest that FENO varies with the severity of airway inflammation and may therefore provide a useful marker of disease severity.

Proof of concept studies suggest that adjusting ICS dose according to monitored airway inflammation might improve clinical outcomes in asthma. Individual studies have suggested FENO monitoring results in fewer exacerbations [2], lower corticosteroid requirements [13], reduced airway responsiveness [14] and improved lung function [15]. However, a recent meta-analysis concluded that, although interventions based upon FENO reduce corticosteroid use in adults, FENO-monitoring drives up corticosteroid doses in children [16]. Exacerbation frequency was not significantly affected in either children or adults [16].

Previous studies have shown FENO to add little to asthma management [13-15;17-18]; this might reflect problems with patient selection, dose-adjustment protocol, or the frequency of FENO monitoring or corticosteroid dose adjustment. Few previous studies focused upon moderate-severe asthma. Studies of mild-moderate asthma may have been underpowered with respect to exacerbations. This prospective, randomised, double-blind study was designed to be pragmatic, reflecting actual clinical management in paediatric outpatients, and aimed to assess whether FENO-directed therapy can reduce ICS dose or exacerbation frequency.

METHODS

Participants

Participants were recruited from outpatient clinics at Southampton University Hospital, St Mary's Hospital, Portsmouth, St Mary's Hospital, Isle of Wight and the Royal Hampshire County Hospital, Winchester. Inclusion criteria were age 6-17 years, clinical diagnosis of asthma and treatment with ≥400 mcg/day beclomethasone/budesonide or ≥200 mcg/day fluticasone. Asthma diagnosis was based upon a history of typical symptoms, ≥ 15% increase in forced expiratory volume in 1 second (FEV_1) with bronchodilator or diurnal peak expiratory flow (PEF) variability ≥ 15% [19]. Exclusion criteria were inability to perform spirometry or FENO measurement, cigarette smoking, poor treatment adherence, life-threatening exacerbation or need for maintenance oral prednisolone.

Protocol

Participants completed a PEF diary, a paediatric asthma quality of life assessment (PADQLQ) [20], and underwent aeroallergen skin prick testing (house dust mite, grass pollens, tree pollens, cat and dog; ALK-Abelló, Hørsholm, Denmark). Participants with a clinical history of IgE-mediated food allergy, rhinitis or eczema, or one or more skin prick tests ≥ 3mm diameter were considered atopic. Participants' asthma was stabilised if necessary over 4-16 weeks prior to randomisation. Computer-generated random numbers were used to assign participants at enrolment to either FENO-based or standard management. Participants were block randomised according to recruitment centre and randomisation was stratified by inhaled corticosteroid dose (400-800 mcg/day or > 800 mcg/day beclomethasone equivalent). Group allocation was recorded by a research nurse and communicated to an independent clinician responsible for therapy decisions. All participants were assessed identically at each

subsequent visit so that participants and the medical staff assessing asthma control were unaware of group allocation. Participants were assessed 2-monthly for 12 months.

At each visit, a single measure of FENO (blinded to the patient, family and assessing clinician) was taken by a research nurse according to ATS/ERS guidelines, using a portable monitor (NIOX MINO; Aerocrine, Solna, Sweden) [6, 21]. After FENO measurement, FEV_1 was measured according to ATS/ERS guidelines [22] using a portable spirometer (KoKo version 4; PDS Instrumentation; Louisville, USA). Finally, an assessing clinician (blinded to allocation group and FENO) assessed treatment adherence by direct questioning, recorded exacerbations and administered a questionnaire reviewing symptoms and reliever use over the preceding two months [modified from 23].

Exacerbations were defined as ≥ 48 hours of increased asthma symptoms or therapy, or decreased PEF (≥ 25%) and classified as mild (requiring increased bronchodilator therapy only); moderate (requiring systemic corticosteroids); or severe (requiring ≥ 8 hours admission) [modified from 13, 24]. The blinded clinician categorised participants' asthma as well controlled (symptoms and reliever inhaler < 1 per week and $FEV_1 \geq 90\%$ predicted); controlled (symptoms or reliever inhaler use 1-2 days per week, or $FEV_1 \geq 80\%$ predicted), or poorly controlled (symptoms or reliever inhaler use > 2 days per week, or $FEV_1 < 80\%$ predicted) [modified from 13].

Therapy decisions were taken by a clinician independent of participant assessment following a simple algorithm reflecting symptom control for standard management subjects, and FENO measurements in addition to symptom control for the FENO group (Table 1). Under standard management, therapy was increased if symptoms were poorly controlled and decreased if

symptoms were well controlled for 3 months as per the SIGN/BTS guidelines [25](Table 2). In the FENO group levels of FENO guided therapy. ICS was decreased if FENO ≤ 15ppb and symptoms were controlled or well controlled for 3 months in similar steps as for the standard management group. Where asthma was poorly controlled and FENO was < 25ppb in the FENO group, long-acting beta-agonist (LABA) therapy was maximised before ICS were increase. ICS was increased if FENO ≥ 25ppb or FENO doubled from baseline. If FENO remained raised after increasing by two SIGN/BTS steps, ICS was not further increased unless participants were poorly controlled.

Statistical analysis

Change in ICS dose and exacerbation frequency over 12-month's follow-up was compared between FENO and standard management according to intention to treat. Corticosteroid doses were calculated as beclomethasone equivalents (mcg). For subjects with incomplete follow-up, the number of exacerbations was divided by the number of months' participation then multiplied by 12 to provide 12 month's data. Two sample t-tests were used for normally distributed data, otherwise two sample Mann-Whitney rank-sum tests were undertaken. A 5% significance level was used throughout. Planned secondary analyses were performed: (1) per protocol analysis restricted to subjects with complete follow-up and (2) analysis considering restricted to participants with atopic asthma. Stata® 11 (Stata Corp., College Station, TX) was used for all analyses.

We calculated that data from 90 subjects would provide power to detect the difference between a 200 and 100 mcg reduction (SD 150 mcg) in inhaled corticosteroid dose in the two groups assuming 80% power and < 5% significance level. There would also be 80% power to detect a 20% reduction in exacerbation frequency in the FENO group assuming 2

exacerbations per year (SD 0.75) in the standard management group.

RESULTS

Of the 96 children screened, 90 met the inclusion criteria (Figure 1) and were randomised; 44 to FENO-based (49%) and 46 to standard management (51%). The two groups were well matched at baseline for demographic and clinical features (Table 3). Thirteen (14%) participants had incomplete follow-up; ten from the FENO group and three under standard management. Eleven participants withdrew at their request, one was withdrawn due to non-adherence, and one following a life-threatening exacerbation (Figure 1). The groups remained well matched when subjects with incomplete follow-up were excluded (data not shown).

In total 584 visits were conducted, symptoms were assessed as controlled on 348 occasions (59.6%), well controlled on 115 (19.7%) and poorly controlled on 121 (20.7%). Therapy was unchanged on 365 visits (62.5%), increased on 129 (22.1%) and decreased on 90 (15.4%). When therapy was increased in the FENO group this reflected FENO alone on 44 occasions (50.0%), symptoms alone on 13 occasions (14.8%) and on 31 occasions (35.2%) both elevated FENO and poor control was recorded. Of the 43 therapy reductions observed in the standard management group 25 occurred with FENO > 15 ppb and would not have occurred had the participant been allocated to the FENO group.

Inhaled corticosteroid dose

As ICS data were highly skewed, median values are reported and non-parametric tests applied. ICS dose did not change significantly between initial and final visit in either group (FENO p=0.901, Standard p=0.498) (Table 4). There was no significant difference between groups in ICS dose at either the initial (visit 0) or final visit (visit 6), nor in change of ICS dose during the trial (Figure 2 and Table 4). Thirty-four children in the FENO group and 43 under standard management completed 12 months' follow-up. When analysis was restricted

to participants with complete follow-up, the ICS dose change was not significantly different between groups (p=0.670) and there was no significant between group difference in total ICS dose received during follow-up (data not shown). Similarly, no between group difference in ICS dose change was seen after restricting the analysis to the 68 children who were atopic (p=0.129) (data not shown).

Exacerbation frequency

Thirty seven subjects in the FENO group (84.1%) and 38 in the standard group (82.6%) experienced at least one exacerbation during follow-up. Of these, five in the FENO (11.4%) and three in the standard group (6.5%) experienced a severe exacerbation. The number of subjects experiencing an exacerbation did not differ between groups (p=0.850) (Table 4); neither was there a difference between the groups regarding the number of subjects experiencing a severe exacerbation (p=0.420). Time to first exacerbation did not differ between groups (p=0.391) (Figure 3). There were no significant between group differences for either overall exacerbation frequency or for frequency of mild, moderate or severe exacerbations.

There was no between group difference in exacerbation frequency when in order to avoid the possible complication of seasonality of exacerbations the analysis was restricted to children with complete follow-up (data not shown). Moreover there was no between group difference when the analysis was restricted to atopic children (data not shown).

FENO and lung function

FENO measurements were compared between groups. Neither group experienced a significant change in FENO during follow-up (mean (95% CI) +3.1 ppb (−5.5 - +11.6 ppb)

FENO and +3.3 ppb (−8.5 - +15.1 ppb) standard group). There were no significant between group difference in FENO at any study visit (including baseline) (Figure 4), or in change in FENO during follow-up. Neither FEV_1, FVC nor $FEF_{25-75\%}$ change during follow-up differed significantly between groups (data not shown).

DISCUSSION

Neither inhaled corticosteroid therapy nor exacerbation frequency differed significantly between children with moderate-severe asthma randomised to either standard or FENO-based management. The two groups did not differ according to either total ICS dose received or change in dose over 12 months' follow-up. Moreover, neither group showed a significant reduction in ICS. Exacerbation frequency did not differ significantly between the two groups irrespective of whether exacerbations were or were not associated with an URTI. Similar results were found in a planned subgroup analysis restricted to atopic participants, although power may have been limited by the smaller numbers included in this analysis.

Inhaled corticosteroid dose

FENO monitoring theoretically offers a means of matching ICS to eosinophilic inflammation. Adult studies have shown some reduction in corticosteroid dose with a FENO-based strategy [2]. Conversely, significantly increased corticosteroid doses have been found in paediatric studies [15;17]. In this study, although neither the total ICS dose nor change in dose over 12 months' follow-up differed significantly according to management group, non-significant differences were seen supporting higher ICS prescription in the FENO group. Lower doses in the standard management group may have occurred in part as a consequence of the protocol design; dose reduction in the FENO arm required both low FENO and good symptom control, whilst good symptom control alone was sufficient for dose reduction under standard management. In contrast, the adult study which detected a reduction in corticosteroid dose in the FENO arm followed a protocol whereby the dose increased in the FENO group only if FENO rose above threshold, whilst under standard management any of five control-based criteria triggered a dose increase [13].

Exacerbation frequency

Whilst conventional markers of asthma control poorly predict exacerbations, there is some evidence that exacerbations can be predicted using FENO [26]. It has been hypothesised that FENO-based interventions might tailor inhaled corticosteroid dose in a manner which reduces exacerbations. Decreased exacerbations might justify small increases in ICS dose. Whilst paediatric patients assigned to FENO-based management have been shown to be at reduced risk of requiring one or more oral steroid course [17], only two adult studies have shown a statistically significant reduction in exacerbation frequency [27, 28]. Previous paediatric studies have generally recruited relatively mild asthmatics who would be expected to experience infrequent exacerbations. This study recruited moderate-severe asthmatics in whom a higher frequency of exacerbations could be expected. Follow-up at 2-monthly intervals reflected a compromise between providing adequate opportunity for dose modification and avoiding non-specific reduction of exacerbation frequency across both groups consequent upon regular follow-up. Exacerbation frequency in this study was greater than that in many previous studies but, despite this, reduced exacerbation frequency was not seen in the FENO group. This may reflect greater control in closely monitored participants; the exacerbation frequency was lower in both groups than that reported for the previous year and this may have limited the possibility for further improvement by FENO-monitoring.

Strengths and limitations of this study

This study employed a pragmatic design to reflect clinical management of moderate-severe asthma in paediatric outpatients. Almost 100 children were recruited and participants in this study had a greater severity of asthma compared to similar trials. Treatment adherence was emphasised at each visit. Two cut-offs were used to up- and down-titrate ICS according to FENO level, using a similar protocol, the successful adult trial in pregnant women [27], and

provision was made within the protocol to prevent dose escalation at high FENO levels. The two groups were well matched for clinical and demographic features; although the standard management group contained more males and its members had more past hospital admissions, neither of these factors was significantly associated with the main outcomes and therefore they were unlikely be confounders. By chance, the median FENO level was lower in those randomised to the FENO group but this difference was not statistically significant. As the range of participants' FENO values in each group wide and almost entirely overlapping, this is unlikely to have biased the study results.

Given the theoretical advantage of tailored ICS the lack of empirical support for FENO-based interventions is unexpected. It may be argued that, as FENO levels were not significantly decreased in the FENO group during this study, airway inflammation was not effectively suppressed. Constant low FENO, however, is not necessarily the aim of FENO-based monitoring; rather variation in FENO might reflect variation in airway inflammation thereby improving ICS prescription by providing more sensitive dose titration than that based upon conventional markers of asthma control. Further explanations are required for the inability to demonstrate a clinically useful effect of FENO monitoring.

Aspects of protocol design might in part be responsible for lack of success in this and previous studies [13-15, 16,17]. For example, the long run-in period in this study may have optimised management thereby limiting further improvement. FENO-driven therapy may have been more effective if the study had been restricted to atopic-asthma [29]. Choice of FENO cut-off or the frequency of monitoring and dose adjustment might also affect study outcomes. There may be a need for ICS dosages to be increased more dramatically in the face of a high FENO level to adequately suppress airway inflammation. Disappointingly, however,

studies using intensive telemonitoring [18] or sophisticated multi-level FENO cut-offs [17] to address these issues have failed to reveal a benefit associated with FENO monitoring.

It is becoming evident that factors other than protocol design might account for the lack of success of this and similar studies. Given that sputum eosinophil-based management has been used successfully to reduce exacerbations [2], it is possible that FENO-based strategies are unsuccessful because FENO does inaccurately represents eosinophilic inflammation. Moreover, we now know that FENO provides little useful information regarding non-eosinophilic inflammation, for example high levels of neutrophilic inflammation may be associated with reduced FENO independent of eosinophil number [30]. We have recently shown that FENO has been shown to correlate more closely with atopy than with asthma and to vary little with increasing frequency of wheezing attacks in non-atopic asthmatics [29]. It appears that high FENO levels in some individuals cannot be reduced by higher corticosteroid doses [31], possibly because of retrograde flow in association with severe rhinitis. These findings suggest that FENO is influenced by factors other than asthma and that in some patients, non-invasive markers of airway inflammation are disconnected from asthma symptoms [32]. Together these factors suggest the efficacy of FENO-guided strategies may vary according to the population in which they are employed and cast doubt upon the appropriateness of pre-defined FENO cut-offs.

Empirical support for FENO-based management has been found in atopic and in obese subjects [17]. This study considered the issue of atopy but was not adequately powered to support sub-analyses. Theoretically increased effectiveness compared to conventional management might be expected in subjects discordant for FENO levels and symptoms. Patients who show an increase in FENO following ICS reduction whilst experiencing no

immediate deterioration in symptoms might represent a subgroup in which FENO-based management is most successful, identifying and randomising such individuals might represent an optimal trial paradigm.

The FENO cut-off used to direct treatment decisions is critical and may explain differences seen between studies; too low a cut-off predisposes to higher inhaled corticosteroid doses in the FENO group whilst too high might fail to reduce exacerbation frequency. FENO standardised by an individual's previous best value has been demonstrated to correlate with asthma control [9]. An alternative to pre-defined cut-offs might be to adjust corticosteroid dose according to an individual's personal best FENO level; this has yet to be assessed.

Conclusions

No difference was found in either the inhaled corticosteroid dose or the exacerbation frequency between children with moderate-severe asthma randomised to either standard or FENO-based management. Furthermore, no particular benefit was found for atopic children. At present there is little evidence to support the use of FENO monitoring in routine outpatient management of paediatric asthma.

ABBREVIATIONS

FENO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
ICS	Inhaled corticosteroid therapy
IQR	Interquartile range
LABA	Long-acting beta-agonist
PAQLQ	Paediatric asthma quality of life assessment

PEF Peak expiratory flow

COMPETING INTERESTS: None

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REFERENCES

1. Synek M, Beasley R, Frew AJ, et al. Cellular infiltration of the airways in asthma of varying severity. Am J Respir Crit Care Med 1996: 154: 224-230.

2. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002: 360: 1718.

3. Vignola AM, Rennar SI, Hargreave FE, et al. Standardised methodology of sputum induction and processing. Future directions. Eur Respir J 2002: 37: 51s-55s.

4. Wilson NM, James A, Uasuf C, et al. Asthma severity and inflammation markers in children. Pediatr Allergy Immunol 2001: 12: 125-132.

5. Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. Am J Respir Crit Care Med 2000: 161: 64-72.

6. Baraldi E, de Jongste JC. European Respiratory Society, & American Thoracic Society 2002, Measurement of exhaled nitric oxide in children. Eur Respir J. 2001: 20(1): 223-237.

7. Baraldi E, Carrà S, Dario C, et al. Effect of natural grass pollen exposure on exhaled nitric oxide in asthmatic children. Am J Respir Crit Care Med 1999: 159: 262-266.

8. Brussee JE, Smit HA, Kerkhof M, et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. Eur Respir J 2005: 25: 455-461.

9. Roberts G, Hurley C, Bush A, Lack G. Longitudinal study of grass pollen exposure, symptoms, and exhaled nitric oxide in childhood seasonal allergic asthma. Thorax 2004: 59(9): 752-756.

10. Sippel JM, HoldenWE, Tilles SA, et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. J Allergy Clin Immunol 2000: 106: 645-650.

11. Frank TL, Adisesh A, Pickering AC, et al. Relationship between exhaled nitric oxide and childhood asthma. Am J Respir Crit Care Med 1998: 158: 1032-1036.

12. Baraldi E, Azzolin NM, Zanconato S, Dario C, Zacchello F. Corticosteroids decrease exhaled nitric oxide in children with acute asthma. J Pediatr 1997: 131: 381-385.

13. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma. N Engl J Med 2005: 352: 2163-2173.

14. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC.Titrating steroids on exhaled nitric oxide in asthmatic children: a randomized controlled trial. Am J Respir Crit Care Med 2005: 172: 831-836.

15. Fritsch M, Uxa S, Horak F Jr, et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. Pediatr pulmonol 2006: 41: 855-862.

16. Petsky HL, Cates CJ, Li AM, Kynaston JA, Turner C, Chang AB Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev 2009, Issue 4. Art. No.: CD006340. DOI: 10.1002/14651858.CD006340.pub3.

17. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet 2008: 372: 1065-1072.

18. De Jongste JC, Carraro S, Hop WC, Baraldi E; CHARISM Study Group. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. Am J Respir Crit Care Med 2009: 179: 93-97.

19. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987: 136:225-244.

20. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res 1996: 5: 35-46.

21. Selby A, Clayton B, Grundy J, Pike K, Drew K, Raza A, Kurukulaaratchy R, Arshad SH, Roberts G. Are exhaled nitric oxide measurements using the portable NIOX MINO® repeatable across age, gender and lung function? Respiratory Research 2010; 11:43

22. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry, Eur Respir J. 2005: 26(2): 319-338.

23. Wasserfallen JB, Gold K, Schulman KA, Baraniuk JN. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. J Allergy Clin Immunol 1997: 100: 16-22.

24. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma. The OPTIMA Randomized Trial. Am J Respir Crit Care Med 2001: 164: 1392-1397.

25. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British guidelines on the management of asthma. Thorax 2003: 58(Suppl I): i1-94.

26. Zacharasiewicz A, Wilson N, Lex C, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. Am J Respir Crit Care Med 2005: 171: 1077-1082.

27. Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, Clifton VL, Gibson PG. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. The Lancet 2011; 378: 983 – 990.

28. Malerba M, Ragnoli B, Radaeli A, Tantucci C. Usefulness of Exhaled Nitric Oxide and Sputum Eosinophils in the Long-term Control of Eosinophilic Asthma. Chest 2008:134(4)733-739.

29. Scott M, Raza A, Karmaus W, et al. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study.Thorax. 2010: 65(3): 258-262.

30 Tseliou E; Bessa V; Hillas G, et a. Exhaled Nitric Oxide and Exhaled Breath Condensate pH in Severe Refractory Asthma. Chest 2010; 138(1):107–113.

31. Pijnenburg MWH, Bakker EM, Lever S, Hop WC, de Jongste JC. High fractional concentration of nitric oxide in exhaled air despite steroid treatment in asthmatic children. Clin Exp Allergy 2005: 35: 920-925.

32. Haldar P, Pavord ID, Shaw D, et al.Cluster Analysis and Clinical Asthma Phenotypes Am. J. Respir. Crit. Care Med 2008: 178(3): 218-224.

Figure 1 Flow of participants through the study, comparison of numbers in the FENO and standard management groups

Incomplete follow up in FENO group: two dropped out after visit 1, two after visit 2, three after visit 3 (one with a life threatening exacerbation and one due to non-compliance), one after visit 4 and two after visit 5. In the standard management group, one participant dropped out after visits 3, 4 and 5.

Figure 2 Inhaled corticosteroid dose at each visit according to randomisation to either FENO or standard management group

Points represent median inhaled corticosteroid dose in beclomethasone equivalents (mcg) at each visit for each group while the bars represent the interquartile range.

Figure 3 Kaplan-Meier survival estimates comparing time to first exacerbation in days for subjects in the Standard and FENO management groups

Curve represents the proportion of participants in each group who have not experienced an exacerbation at each time point.

Figure 4 FENO measurements at each visit according to randomisation to either FENO or standard management group.

Points are geometric mean measurements for each group at each visit with bars representing 95% confidence intervals.

Table 1. Algorithm for managing asthma

FENO group			
FENO level	Poorly controlled asthma	Asthma controlled	Well controlled asthma
≥25ppb or FENO more than twice baseline	Increase inhaled corticosteroids or add LTRA if already at BTS/SIGN* step 4 If after increasing by two BTS/SIGN* steps FENO remains high do not increase therapy further	Increase inhaled corticosteroids or add LTRA if already at BTS/SIGN* step 4	
>15 to <25ppb	Increase LABA therapy; if dose maximal, increase corticosteroids or add LTRA if already at BTS/SIGN* step 4	Continue current treatment	
≤15ppb	Increase LABA; if dose maximal, increase corticosteroids or add LTRA if already at BTS/SIGN* step 4	If asthma controlled for 3 months, reduce inhaled corticosteroids; if dose ≤400mcg, reduce LABA	
Standard management group			
Poorly controlled asthma		Asthma controlled	Well controlled asthma
Increase inhaled corticosteroids or add LABA and/or LTRA as directed by stepwise approach to therapy BTS/SIGN*		No change in inhaled corticosteroids	If well controlled for 3 months, reduce inhaled corticosteroids; if dose ≤400mcg, reduce LABA

*United Kingdom guidelines on asthma [25]. Levels of asthma therapy are detailed in Table 2. LABA: long-acting bronchodilator; LTRA: leukotriene receptor antagonist.

Table 2 Asthma therapy levels

Step	Option 1	Option2	Option3
1	No inhaled corticosteroid	No inhaled corticosteroid	No inhaled corticosteroid
2	Beclometasone 50mcg twice a day via spacer	Budesonide 50mcg twice a day via spacer (or turbohaler)	Fluticasone 50mcg once a day via spacer (or accuhaler)
3	Beclometasone 100mcg twice a day via spacer	Budesonide 100mcg twice a day via spacer (or turbohaler)	Fluticasone 50mcg twice a day via spacer (or accuhaler)
4	Beclomethasone 200mcg twice a day via spacer	Budesonide 200mcg twice a day via spacer (or turbohaler)	Fluticasone 100mcg twice a day via spacer (or accuhaler)
5	Trial of LABA. If ineffective, consider trial of LTRA.	Trial of LABA. If ineffective, consider trial of LTRA.	Trial of LABA. If ineffective, consider trial of LTRA.
6	Fluticasone 125mcg twice a day via spacer	Fluticasone 125mcg twice a day via spacer	Fluticasone 125mcg twice a day via spacer
7	Fluticasone 250mcg twice a day via spacer	Fluticasone 250mcg twice a day via spacer	Fluticasone 250mcg twice a day via spacer
8	Consider short course of prednisolone or other therapeutic options.	Consider short course of prednisolone or other therapeutic options.	Consider short course of prednisolone or other therapeutic options.

Levels of asthma therapy. Modified from British guidelines on the management of asthma [25]. LABA: long-acting bronchodilator. LTRA: leukotriene receptor antagonist.

Table 3 Comparison of the baseline demographic and clinical features of children in the FENO and standard management groups.

	FENO group (n=44)	Standard management group (n=46)	p-value
Demographics			
Age years mean (SD)	10.51 (2.62)	11.42 (2.69)	0.107
Male gender (%)	21 (47.7%)	30 (65.2%)	0.094
Gestation weeks median (IQR)	40 (38-41)	40 (38-40)	0.137
Median birth weight in kg (IQR)	3.23 (2.72-3.52)	3.29 (2.81-3.57)	0.924
Caucasian ethnicity (%)	41 (93.2%)	44 (95.7%)	0.609
Recruited from tertiary centre (%)	28 (63.6%)	30 (65.2%)	0.984
Age at diagnosis in years median (IQR)	1 (1 – 2)	2 (1 – 2)	0.514
History of severity			
Median exacerbations in last year (IQR)	3.5 (2 – 8)	4.5 (2 – 7)	0.519
Median oral corticosteroids courses last year (IQR)	1 (0 – 3.5)	2 (0 – 3)	0.549
Median number of hospital admissions ever (IQR)	2 (0 – 5)	4 (1 – 8)	0.096
Risk factors and exposures			
Maternal asthma (%)	18 (40.9%)	12 (26.1%)	0.136
Father asthma (%)	15 (34.1%)	13 (28.3%)	0.550
Household smoke exposure (%)	4 (9.1%)	6 (13.0%)	0.551
Atopy (%)	30 (81.1%)	38 (88.4%)	0.363
Baseline status and treatment			
Median PADQLQ (IQR)	130.5 (101.0-145.0)	125.0 (113.0-142.0)	0.936
Asthma uncontrolled at screening (%)	12 (27.3%)	16 (34.8%)	0.709

Mean baseline FEV_1 (SD)	87.2 (15.3)	91.1 (13.2)	0.193
Mean FEV_1 reversibility (SD)	6.39% (6.24)	6.96% (6.67)	0.677
Median initial beclomethasone equivalent (IQR)	750 (400-1000)	800 (400-1000)	0.629
Prescribed serevent/eformetol (%)	32 (72.7%)	36 (78.3%)	0.541
Prescribed montelukast (%)	22 (50.0%)	24 (52.2%)	0.837
Prescribed theophylline (%)	4 (9.1%)	2 (4.4%)	0.367
Prescribed omalizumab (%)	0 (0%)	0 (0%)	

For continuous outcomes, means were compared by t-tests unless the data were skewed when non-parametric tests were used. Chi-squared tests were used to compare categorical outcomes. PADQLQ: Paediatric quality of life questionnaire score. IQR: interquartile range.

Table 4 Comparison of inhaled steroid therapy and annual exacerbation frequency in the FENO and standard therapy groups.

	Median initial corticosteroid dose (IQR)	Median final corticosteroid dose (IQR)	Median corticosteroid dose change (IQR)	Median total corticosteroid dose (IQR)	Median number of exacerbations (IQR)	Perentage of subjects with exacerbations
FENO group	750 (400 to 1000)	800 (400 to 1000)	0 (−200 to 300)	264,800 (164,400 to 350,000)	3 (1-5)	84.1
Standard management	800 (400 to 1000)	500 (400 to 1000)	0 (−300 to 0)	249,600 (140,000 to 365,300)	2 (1-4)	82.6
P-value	0.629	0.543	0.297	0.555	0.290	0.850

Table includes data from all 90 randomised subjects. All doses are beclomethasone equivalents in micrograms. Median change in corticosteroid dose is the median of the differences between the doses at the initial and final visits. The total corticosteroid dose is the total dose received during 12 months follow-up assuming the dose reported at each visit accurately represents that taken for the preceding 2 months and extrapolating where necessary from the final dose in cases of incomplete follow-up. Exacerbation data was also extrapolated where a participant did not provide 12 months of data. P-values represent a two sample Mann-Whitney rank-sum test of the between groups difference of exacerbation frequency and chi-squared test for percentage in each group experiencing exacerbation.