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Fractional exhaled nitric oxide for the management of asthma in adults: a systematic review

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ABSTRACT The aim of this review was to evaluate the clinical effectiveness of fractional exhaled nitric oxide (F_{ENO}) measured in a clinical setting for the management of asthma in adults.

13 electronic databases were searched and studies were selected against predefined inclusion criteria. Quality assessment was conducted using QUADAS-2. Class effect meta-analyses were performed.

Six studies were included. Despite high levels of heterogeneity in multiple study characteristics, exploratory class effect meta-analyses were conducted. Four studies reported a wider definition of exacerbation rates (major or severe exacerbation) with a pooled rate ratio of 0.80 (95% CI 0.63–1.02). Two studies reported rates of severe exacerbations (requiring oral corticosteroid use) with a pooled rate ratio of 0.89 (95% CI 0.43–1.72). Inhaled corticosteroid use was reported by four studies, with a pooled standardised mean difference of −0.24 (95% CI −0.56–0.07). No statistically significant differences for health-related quality of life or asthma control were found.

F_{ENO} guided management showed no statistically significant benefit in terms of severe exacerbations or inhaled corticosteroid use, but showed a statistically significant reduction in exacerbations of any severity. However, further research is warranted to clearly define which management protocols (including cut-off points) offer best efficacy and which patient groups would benefit the most.

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Introduction

Asthma is a chronic disorder of the airways, caused primarily by inflammatory processes and bronchoconstriction. Poorly controlled asthma can have a significant impact on the quality of life of the affected individual and their family. An estimated 5.4 million people in the UK are currently receiving treatment for asthma [1, 2]. Despite the high prevalence rates, deaths resulting from asthma are uncommon.

The pharmacological management of asthma in adults aims to control symptoms (including nocturnal symptoms and exercise induced asthma), prevent exacerbations and achieve the best possible lung function, with minimal side-effects of treatment. Inhaled corticosteroids (ICSs) are the main treatment for asthma, and although at low dosage the side-effects are few, high dosage or long-term use of ICS is associated with an increased risk of systemic side-effects [3]. The current British guidelines on the management of asthma recommend a stepwise approach, with escalation of medication until control is reached or stepping down when control is good [4]. However, in certain cases there is suspected over- and under-treatment.

Fractional exhaled nitric oxide ($F_{E}NO$) is a noninvasive biomarker of airway inflammation in asthma. High $F_{E}NO$ in the breath of patients with symptoms of asthma are correlated with eosinophilic airway inflammation (a distinct corticosteroid responsive phenotype of asthma) [5–7]. The presence of eosinophils may be used to direct treatment as patients without eosinophilic inflammation are thought to be less responsive to ICS treatment [8]. Therefore, in order to reach a balance between treatment and control, the addition of $F_{E}NO$ monitoring might allow optimisation of treatment in the different disease phenotypes. Existing reviews of $F_{E}NO$ monitors suggest some benefits associated with $F_{E}NO$ [9–11]; however, none were statistically conclusive. In addition, these reviews focused on number of people with an exacerbation, inappropriately included the cohort of pregnant women in the meta-analysis (pregnancy can substantially affect the course of asthma) [12] and are out-of-date. To address these limitations we have updated an existing review [9], with the addition of three new studies [13–16], to determine the potential role of $F_{E}NO$ monitors in the management and monitoring of asthma in adults. This systematic review was undertaken to inform a UK National Institute for Health and Care Excellence appraisal which included an assessment of the use of the electrochemical $F_{E}NO$ monitors NIOX MINO (Aerocrine AB, Solna, Sweden), NIOX VERO (Aerocrine AB) and NObreath (Bedfont Scientific Ltd, Maidstone, UK) in the diagnosis and management of asthma [17, 18].

Methods

A systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [19].

Data sources and searches

13 electronic databases and research registers were searched (including MEDLINE and the Cochrane Library) between March and April 2013, with update searches conducted in September 2013 and November 2014. Terms for NIOX VERO, a new $F_{E}NO$ device, were added to the strategy in August 2013. The search strategy used free-text terms and subject headings for the tests (*e.g.* NIOX MINO, NObreath and $F_{E}NO$) combined with keywords for the condition (*i.e.* asthma or lower respiratory tract symptoms). No language restrictions were applied. As part of updating an earlier systematic review [9], searches were limited by date from 2009 (the last search date from the earlier review). Searches were supplemented by hand-searching reference lists of relevant studies and contact with experts in the field. Further details of the search strategy are provided in the online supplementary appendix 1.

Study selection

All titles were examined for inclusion by one reviewer and any citations that did not meet the inclusion criteria (*e.g.* non-human or unrelated to asthma) were excluded. All abstracts and full-text articles were then examined independently by two reviewers. Any disagreements in the selection process were resolved through discussion. Details of the selection criteria are provided in table 1. This review focuses on studies relating to adults only. Details of $F_{E}NO$ for the management of asthma in children have been published elsewhere [21].

Data abstraction

Data relating to study design, patient characteristics and outcomes were extracted by one reviewer into a standardised data extraction form and independently checked for accuracy by a second reviewer. Any discrepancies were resolved through discussion. Where necessary, study authors were contacted for missing information or additional data.

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TABLE 1 Study selection criteria

	Inclusion	Exclusion
Population	Adults (⩾18 years) with diagnosis of asthma including pregnant women.	Studies that included cohorts with a mean age <18 years of age Recruited patients were not diagnosed with asthma Animal models Unselected specific population (*e.g.* firefighters, obese or athletes)
Intervention	Studies that measured F_{ENO} according to the ATS 2005 criteria [20] for the management of asthma, either with or without other indicators of asthma control. ATS criteria relating to multiple testing were relaxed to allow inclusion of studies that operated electrochemical devices in line with the manufacturer's instructions, which state only one test is required. Studies where monitoring was performed at home were excluded as this was not within the scope of the assessment.	Device which is not validated for measuring F_{ENO} Offline measurements Studies where F_{ENO} is measured on a more regular basis (*i.e.* not during a routine annual review)
Comparator	Studies comparing the intervention to any other management strategy that does not utilise F_{ENO} measurements.	Includes the use of F_{ENO} measurement as part of the management strategy
Outcome	Primary outcome of interest included incidence of acute exacerbation (any definition of exacerbation severity was acceptable, including "use of oral corticosteroids"), inhaled corticosteroid use, unscheduled contact with healthcare officials, hospitalisations and emergency department visits expressed or calculable as rates per person year or as the number of patients experiencing exacerbations. These outcomes were chosen as they have the greatest impact both clinically and economically. Other outcomes included clinical complications associated with acute exacerbation, asthma control and symptoms, adverse events, health-related quality of life, mortality and compliance.	Does not report data on F_{ENO}-guided step-up/step-down therapy Measure of alveolar nitric oxide or nasal nitric oxide
Study type	Randomised controlled trials.	Preclinical and biological studies Editorials and opinion pieces Studies only published in languages other than English

F_{ENO}: fractional exhaled nitric oxide; ATS: American Thoracic Society.

Assessment of methodological quality

The methodological quality of each included study was assessed according to the Cochrane Collaboration's tool for assessing the risk of bias in randomised controlled trials (RCTs) [22]. The studies were assessed by one reviewer and independently checked by another.

Data synthesis and analysis

Data were tabulated and discussed in a narrative review. Meta-analyses were planned, where appropriate, to estimate a summary measure of effect on relevant outcomes using the methods documented in the Cochrane Handbook [22, 23]. For rate outcomes, rates per person year were the preferred outcome metric, as this accounts for multiple events in a single patient. The generic inverse variance method was used to meta-analyse rate ratios using Review Manager software (Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For continuous outcomes, a standardised mean difference analysis was conducted where outcomes were not reported in a standardised way. In all cases, fixed effects were used first, and random effects applied if the I^2 statistic indicated that heterogeneity was moderate or high. This was judged to be the case at >40%. Studies in pregnant women were analysed separately as F_{ENO} may be affected by pregnancy [12].

TABLE 2 Study and population characteristics

First author [ref.]	Country, funding details	Study design	Inclusion/exclusion criteria	Subjects analysed/ recruited n/N	Age years	Males n/N (%)	Spirometry	Severity	F_{eNO}	Smokers; Atopic; Medication use
Smith [24]	New Zealand, Mixed funding[#] including equipment from Aerocrine	RCT: single blind, single centre, placebo-controlled	Chronic asthma [27] managed in primary care; regular ICS for ⩾6 months, no dose change in previous 6 weeks. If could not tolerate removal of LABA during run-in allowed to participate if could tolerate a fixed dose. Exclusions: ⩾4 courses oral prednisone in previous 12 months; admission to hospital for asthma in previous 6 months; ever admitted to IC for asthma; smokers (current or ex-) with a history of >10 pack-years.	94/110 WBR: 13; Intervention group: 46/48 Control group: 48/49	Mean age 44.8 (range 12–73)	41/110 (37.3%)	Mean (range) FEV_1 % pred Intervention group: 86.4 (80.6–92.2) Control group: 83.1 (76.5–89.7)	Mean (95% CI) symptom score[¶] Intervention group: 0.6 (0.4–0.8) Control group: 0.8(0.6–1.1)	GM (95% CI) F_{eNO} 250 mL^{+} Intervention group: 7.8 (6.6–9.3) Control group: 6.4 (5.5–7.5)	Smokers: None Atopic: NR Medication use: Bronchodilator use, mean per day over the previous 7 days (95% CI) Intervention group: 0.5 (0.2–0.8) Control group: 0.6 (0.3–0.8) ICS use NR
Shaw [25]	UK, Asthma UK grant, speakers fees reported, but not from Aerocrine	RCT: single blind, parallel group	GP diagnosis of asthma with ⩾1 prescription for anti-asthma medication in the past 12 months. Current nonsmokers with a past smoking history of <10 pack-years. Exclusions: poorly compliant; those with a severe asthma exacerbation (needing prednisolone) in the previous 4 weeks.	118 (ITT LOCF)/119 WBR: 1 Intervention group: 58 Control group: 60	Adults >18 years Mean age NR	54/118 (46%)	Mean±SD FEV_1 % pred Intervention group: 81.4±20.9 Control group: 84.9±20.1 Mean±SD FEV_1/FVC Intervention group: 71±10.7 Control group: 72±9.9	Mean±SD Juniper score Intervention group: 1.32±0.65 Control group: 1.26±0.75	GM (68% CI) log F_{eNO} Intervention group: 29.2 (14.0–61.0) Control group: 31.2 (13.3–73.1)	Ex-smokers: Intervention group: 22% Control group: 25% Atopic:78 (66.1%) out of 118 Medication use: Mean±SD ICS daily dose Intervention group: 697±708 µg Control group: 652±533 µg
Syk [14]	Sweden, Mixed funding[#], some from Aerocrine	RCT: open label, parallel group, multicentre	Doctor's diagnosis of asthma and ICS treatment for ⩾ 6 months, IgE sensitisation to at least one major airborne perennial allergen. Nonsmokers for ⩾1 year and with smoking history of <10 pack-years. Patients all had mild to moderate asthma.	165/187 WBR: 6 Intervention group: 87/93 Control group: 78/88	Adults (18–64 years) Mean±SD 41±12.4	94/181 (51.9%)	Mean±SD FEV_1 % pred Intervention group: 84.3±14.1 Control group: 83.7±12.5 Mean±SD FEV_1/FVC Intervention group: 0.78±0.08 Control group: 0.79±0.08	NR	GM (95% CI) F_{eNO} ppb Intervention group: 22.0 (19.3–25.2) Control group: 21.6 (18.7–25.0)	Smokers: None Atopic:165 (100%) out of 165 Medication use: Median (IQR) budesonide equivalent ICS dose 400 (400–800) µg·day^{-1} LABA before study entry 54 (30.0%) out of 180

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TABLE 2 Continued

First author [ref.]	Country, funding details	Study design	Inclusion/exclusion criteria	Subjects analysed/ recruited n/N	Age years	Males n/N (%)	Spirometry	Severity	F_{eNO}	Smokers; Atopic; Medication use
Calhoun [13]	USA, Mixed funding#, equipment from Aerocrine	RCT: multiply-blinded, multicentre study	Mild to moderate asthmatics, well controlled persistent asthma with compliance rates ⩾75%, who could tolerate treatment of two puffs twice daily of beclomethasone HFA (40 μg·puff^{-1}) during the 2 week run-in period.	363 recruited to trial WBR: 21 Intervention group: 115/115§ Control group: 114/114f Other study arm (not included in review): 113/113	Mean±SD: Intervention group: 34.8±11.3; Control group: 34.2±11.9	75/229 (32.8%)	Mean±SD FEV_1 % pred Intervention group: 86.3±10.4 Control group: 87.7±12.1	Mean±SD ACQ score Intervention group: 0.79±0.54 Control group: 0.72±0.50 Mean±SD AQLQ score Intervention group: 6.16±0.77 Control group: 6.27± 0.76 Mean±SD ASUI score Intervention group: 0.88±0.12 Control group: 0.90±0.10	GM±SD F_{eNO} ppb Intervention group: 18.88±0.66 Control group: 21.38±0.62	Smokers: NR Atopic: 196 (85.6%) out of 229 Medication use: Albuterol rescue use median (IQR) Intervention group: 0.07 (0–0.43) Control group: 0.04 (0–0.29)
Honkoop [16]	The Netherlands, Mix of non-commercial grants and funding from Aerocrine	RCT; cluster design	From protocol: doctor's diagnosis of asthma; who need ICS as controller medication (step 2–4 GINA guidelines); ICS ⩾3 months in the previous year; no exacerbation of asthma within 1 month before entry. Exclusions: daily or alternate day oral corticosteroid therapy for at least 1 month before entering into the study.	611 randomised Other data NR Intervention group: 189/205 Controlled asthma: 219/232 Partly controlled asthma: 203/210	Mean±SD age: 39.4±9.5 Intervention group: 39.5±9.3 Controlled asthma: 38.9±9.3 Partly controlled asthma: 39.9±9.8	190/611 (31%) Intervention group: 27.7% Controlled asthma: 31.6% Partly controlled asthma: 34.2%	Mean±SD FEV_1 % pred Intervention group: 93.1±17.0 Controlled asthma: 92.4±17.2 Partly controlled asthma: 93.0±17.0	Mean±SD ACQ score Intervention group: 0.99±0.73 Controlled asthma: 1.08±0.84 Partly controlled asthma: 0.93±0.80	Mean±SD F_{eNO} ppb Intervention group: 24.5±21.7 Controlled asthma: 27.3±30.4 Partly controlled asthma: 24.7±29.8	Smokers: Intervention group: 14% Controlled asthma: 13% Partly controlled asthma: 16% Atopic: 322 (54%) out of 611 Medication use: LABA: Intervention group: 47% Controlled asthma: 49% Partly controlled asthma: 52% Mean±SD beclomethasone equivalent dose: Intervention group: 853±642 μg Controlled asthma: 831±701 μg Partly controlled asthma: 825±639 μg

Continued

TABLE 2 Continued

First author [ref.]	Country, funding details	Study design	Inclusion/exclusion criteria	Subjects analysed/ recruited n/N	Age years	Males n/N (%)	Spirometry	Severity	F_{eNO}	Smokers; Atopic; Medication use
Powell [26]	Australia, Mixed funding, lecture fees from Aerocrine	RCT: double-blind, parallel group, multicentre	Doctor's diagnosis confirmed by respiratory physician's diagnosis of asthma. Nonsmoking pregnant women between 12 and 20 weeks gestation with doctor's diagnosis of asthma and who were using inhaled therapy in last year.	203/242 WBR: 22 Intervention group: 100/111 Control group: 103/109	Pregnant adults >18 years Mean±SD age 28±5.4	0/220 (0%)	Mean (95% CI) FEV_1 % pred Intervention group: 95.1 (92.8–97. 4) Control group: 96.1 (93.5–98.7) Mean (95% CI) FEV_1/FVC Intervention group: 79.7 (75.4–78.0) Control group: 80.63 (79.3–82.0)	Median (IQR) AQLQ-M Intervention group: 0.8 (0.4–1.5) Control group: 1.0 (0.5–1.6) Mean ACQ score (read off graph) Intervention group: 0.98 Control group: 1.01	Median (IQR) F_{eNO} ppb Intervention group: 13.9 (6.6–32.0) Control group: 13.1 (7.5–24.0)	Ex-smokers: 80 (39.4%) out of 203 Atopic: 156 (75.7%) out of 206 Medication use: Median (IQR) days β_2-agonist in the past week Intervention group: 1.0 (0–5) Control group: 2.0 (0–6) ICS users Intervention group: 46 (41.4%) out of 111 Control group: 47 (43.1%) out of 109 Median (IQR) BDP equivalent ICS dose (µg per day) Intervention group: 800 (400–800) Control group: 800 (400–1600)

F_{eNO}: fractional exhaled nitric oxide; RCT: randomised controlled trial; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; IC: intensive care; WBR: withdrew before randomisation; FEV_1: forced expiratory volume in 1 s; GM: geometric mean; NR: not reported; GP: general practitioner; ITT: intention to treat; LOCF: last observation carried forward; FVC: forced vital capacity; IQR: interquartile range; HFA: hydrofluoroalkanes; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ASUI: Asthma Symptom Utility Index; GINA: Global Initiative for Asthma; AQLQ-M; Asthma Quality of Life Questionnaire-Marks; BDP: beclomethasone dipropionate. #: mix of industry and non-industry funding, *e.g.* research council grants. ¶: daily score over the previous 7 days. Asthma symptoms were scored for each 24-h period as follows: 0, indicated no symptoms; 1, symptoms for one short period; 2, symptoms for two or more short periods; 3, symptoms most of the time that did not affect normal daily activities; 4, symptoms most of the time that did affect normal daily activities; and 5, symptoms so severe as to disrupt daily activities. +: F_{eNO} measured at 250 mL·s^{-1} gives lower values than F_{eNO} at 50 mL·s^{-1}. §: 37 withdrew, imputation method NR. f: 13 withdrew, imputation method NR.

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Results

Trial flow

Of the 5354 citations identified, three RCTs [13, 14, 16] met the inclusion criteria and were added to the three existing trials [24–26] identified in the previous systematic reviews [9, 11]. The majority of the excluded articles did not use *F*eNO to guide step-up/step-down therapy or the study design was not an RCT. A summary of the process of identifying and selecting the relevant literature can be found in online supplementary appendix 2.

Characteristics of included studies

Table 2 presents the study characteristics of the six included studies [13, 14, 16, 24–26]. All the included studies compared *F*eNO-guided asthma management to non-*F*eNO-guided management and all patients were recruited in primary care, except for Calhoun *et al.* [13], where the recruitment setting was unclear. The device used to measure *F*eNO was not clearly reported in three studies. Most studies were of a small to moderate size, with the number of patients ranging from 94 [24] to 611 [16]. All studies recruited adults of either sex [13, 14, 16, 24, 25], apart from Powell *et al.* [26], which recruited only pregnant women. The comparability of study populations in terms of severity at baseline is difficult to determine as different scales for severity and different metrics for medication use were reported. Inclusion and exclusion criteria suggest that at least four studies [13, 14, 24, 26] recruited populations with mild to moderate asthma; while the other two studies [16, 25] included a broader spectrum of severity. However, overall the patient population is predominantly milder asthmatics (mean forced expiratory volume in 1 s (FEV_1) range 81–96% predicted). In addition, no studies followed the same timeline, visit frequency, management protocols, number and points of *F*eNO cut-offs, and treatment doses varied across the included studies (table 3).

Risk of bias within studies

Table 4 summarises the methodological quality of the included studies. Generally, two studies [25, 26] performed well receiving a positive assessment of at least six of the seven quality items. The most frequently identified potential sources of a high risk of bias concerned "other biases" related to the receipt of commercial funding (67%) [13, 14, 16, 24]. A high number of publications poorly reported the following aspects: random sequence generation (33%) [13, 24], allocation concealment (33%) [13, 24] and blinding of outcome assessment (50%) [13, 24, 25]. It should be noted that poor performance in quality assessment for the study by Syk *et al.* [14] was due to its open label study design, which was necessary to influence patients' adherence to treatment and to capture these clinically valuable effects.

Outcomes and synthesis of results

Despite wide variation in all aspects of study design across the five studies [13, 14, 16, 24, 25] (excluding the study on pregnant women) [26]; exploratory meta-analyses were conducted where possible for all relevant outcomes (table 5).

Healthcare utilisation

Unscheduled healthcare utilisation, defined as emergency department/accident and emergency visits, out-of-hours general practitioner's surgery visits or hospitalisation, was only reported in Honkoop *et al.* [16]. Although the result showed improvement in healthcare utilisation with *F*eNO management (table 5), this was not statistically significant for all comparisons ($p>0.05$). In the remaining four studies [13, 14, 24, 25], unscheduled healthcare utilisation was included as either treatment failure or severe exacerbations (see later), since exacerbations of asthma can lead to both unscheduled healthcare utilisation and the need for a course of oral corticosteroids (OCSs).

Severe exacerbations

This outcome was defined differently across studies (table 5). Syk *et al.* [14] and Honkoop *et al.* [16] defined it as "worsening requiring a course of OCS"; Shaw *et al.* [25] defined it as "exacerbations resulting in the use of OCS or antibiotics"; and Calhoun *et al.* [13] reported it as "exacerbations", which included exacerbations leading to OCS use, increased ICS use or additional medication for asthma. A meta-analysis of four studies (the study of Smith *et al.* [24] was not included as follow-up data were not calculable as rates per person year) showed that severe exacerbations (while statistically not significant) were less likely in the *F*eNO-guided-management group compared with the control group (figure 1a), with rate ratio of 0.80 (95% CI 0.63–1.02; p=0.08).

Severe exacerbations resulting in the use of OCS

Analysis of studies reporting the number of severe exacerbations resulting in the use of OCS (figure 1b) was limited to only two studies [14, 16], which showed opposite directions of effect. This may be due to variations in the step-up/step-down protocols employed in the studies, or due to the populations being slightly different.

TABLE 3 Description of management strategies

First author [ref.]	Basis for decisions		Treatments indicated	
	Intervention	Control	Intervention	Control
Smith [24]	F_{eNO}, with a safety measure based on symptoms, bronchodilator use and spirometry F_{eNO} <35 ppb (equivalent at 50 mL·s^{-1}) defined as controlled asthma F_{eNO} ⩾35 ppb defined as uncontrolled asthma Safety measure: if one or more of the following clinical criteria are met, increase one step: 1) Symptom score for previous 7 days ⩾1 point more than mean during run-in and minimum score of 2 out of 5 2) Nocturnal wakening on ⩾3 nights per week more than mean during run-in 3) Mean daily bronchodilator use ⩾3 times that of mean during run-in and minimum use of 15 occasions during prior 7 days 4) Diurnal peak flow variation ⩾30% and/or FEV_1 of <85% of baseline	GINA 2002: symptoms, bronchodilator use, spirometer	Dose steps: placebo, inhaled fluticasone 100 µg, 250 µg, 500 µg, 750 µg and 1000 µg Phase 1: until optimal dose reached Phase 2: up titrate one step at a time; down titrate if controlled for two visits, but not lower than optimal dose Patients had personalised self-management plans, which instructed them to take oral prednisone 40 mg per day when morning peak flows fell below 70% of mean run-in values, until it reached >85%, at which time they took 20 mg per day for the same number of days	As for intervention, but without the personalised management plan
Shaw [25]	F_{eNO} plus symptoms (Juniper score) Exhaled nitric oxide <16 ppb on first occasion or exhaled nitric oxide 16–26 ppb on second occasion with 1) Juniper score ⩽1.57: step-down anti-inflammatory treatment, step-down bronchodilator treatment once off steroids. 2) Juniper score >1.57: step-down anti-inflammatory treatment, step-up bronchodilator treatment Exhaled nitric oxide >26 ppb with 1) Juniper score ⩽1.57: step-up anti-inflammatory treatment, no change in bronchodilator treatment 2) Juniper score >1.57: step-up anti-inflammatory treatment, step-up bronchodilator treatment once on maximum anti-inflammatory treatment Safety measure: patients on 2000 µg beclomethasone per day with >26 ppb F_{eNO} and had not fallen to 60% of baseline had sputum checked. If no eosinophilic inflammation, treatment reduced stepwise, unless F_{eNO} increased by >60% of baseline.	BTS/SIGN guidelines using Juniper scale to score symptoms: 1) treatment doubled if score >1.57 2) treatment halved if score <1.57 for 2 consecutive months	Hierarchy of anti-inflammatory treatment: 1) Low dose ICS (100–200 µg BDP twice daily) 2) Moderate dose ICS (200–800 µg BDP twice daily) 3) High dose ICS (800–2000 µg BDP twice daily) 4) High dose ICS (800–2000 µg BDP twice daily) plus LTRA 5) Higher dose ICS (2000 µg BDP twice daily) plus LTRA 6) Higher dose ICS (2000 µg BDP twice daily) plus LTRA plus oral prednisolone 30 mg for 2 weeks, then titrate the dose reducing by 5 mg·week^{-1} Hierarchy of bronchodilator treatment 1) SABA as needed 2) LABA 3) LABA plus theophylline 4) LABA plus theophylline plus nebulised bronchodilator	Step 1: SABA as required Step 2: Add ICS 200–800 µg·day^{-1} BDP equivalent Step 3: Add inhaled LABA Step 4: increase ICS up to 2000 µg·day^{-1} and addition of fourth drug, *e.g.* LTRA, theophylline or LABA Step 5: oral prednisolone, high dose ICS, refer to specialist care

Continued

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TABLE 3 Continued

First author [ref.]	Basis for decisions		Treatments indicated	
	Intervention	Control	Intervention	Control
Syk [14]	F_{ENO} only F_{ENO} <19 ppb (men), <21 ppb (women): decrease one step F_{ENO} 19–23 ppb (men), 21–25 ppb (women): no change F_{ENO} ⩾24 ppb (men), ⩾26 ppb (women): increase one step (no change in treatment step if on step 4 or 5 and using ⩽2 inhalations of SABA per week) F_{ENO} ⩾30 ppb (men), ⩾32 ppb (women): increase two steps (only if on treatment step 1) Grey zone of 5 ppb applied to avoid frequent dose changes	Symptoms, lung function, β-agonist use (usual care)	Steps 1–6: Budesonide (μg·day^{-1}): 0, 200, 400, 800, 800+LTRA, 1600+LTRA Fluticasone (μg·day^{-1}): 0, 100, 250, 500, 500+LTRA, 1000+LTRA Mometasone (μg·day^{-1}): 0, 100, 200, 400, 400+LTRA, 800+LTRA	Assume same doses as intervention
Calhoun [13]	F_{ENO} only Well controlled, F_{ENO} <22 ppb: down one level Controlled, F_{ENO} 22–35 ppb: maintain level Under-controlled, F_{ENO} >35 ppb: up 1 level	NHLBI guidelines (USA version of SIGN guidelines)	Dosing beclomethasone HFA: Level 1=0 μg per day Level 2=80 μg once daily Level 3=160 μg twice daily Level 4=320 μg twice daily Level 5=640 μg twice daily	As intervention
Honkoop [16]	ACQ and F_{ENO} Where ACQ ⩽0.75 with 1) F_{ENO} ⩽25 ppb, step down 2) F_{ENO} >25 ppb and <50 ppb, no change 3) F_{ENO} ⩾50 ppb, step up Where ACQ >0.75 and <1.50 with 1) F_{ENO} ⩽25 ppb: and time <3 months, no change, or change to LABA; if time >3 months, step down ICS 2) F_{ENO} >25 ppb and <50 ppb: step-up (treatment choice) 3) F_{ENO} ⩾50 ppb, step-up ICS by one level Where ACQ ⩾1.50 with 1) F_{ENO} ⩽25 ppb: step-up LABA 2) F_{ENO} >25 ppb and <50 ppb: step-up (treatment choice) 3) F_{ENO} ⩾50 ppb: step-up ICS by two levels	ACQ scores Strict strategy ACQ ⩽0.75: <3 months, no change; > 3 months, step-down ACQ >0.75 and <1.50: Step-up: treatment choice ACQ ⩾1.50: Step-up: treatment choice Sufficient strategy ACQ ⩽0.75: Step-down ACQ >0.75 and <1.50: No change ACQ ⩾1.50: Step-up: treatment choice	Step 1: SABA as needed Step 2: low-dose ICS; or LTRA Step 3: low-dose ICS + LABA; or medium- or high-dose ICS; or low-dose ICS+LTRA Step 4: Add one or more of medium- or high-dose ICS + LABA, and/or LTRA Step 4: Add one or both of OCS (lowest dose), anti-IgE treatment	As intervention for both strategies

Continued

TABLE 3 Continued

First author [ref.]	Basis for decisions		Treatments indicated	
	Intervention	Control	Intervention	Control
Powell [26]	F_{eNO} concentration use to adjust dose of ICS ACQ used to adjust dose of LABA F_{eNO} >29 ppb: ICS increase one step, LABA no change F_{eNO} 16–29 ppb and ACQ ⩽1.5: ICS no change, LABA no change F_{eNO} 16–29 ppb and ACQ >1.5: ICS no change, LABA increase one step F_{eNO} <16 ppb and ACQ ⩽1.5: ICS decrease one step, LABA no change F_{eNO} <16 ppb and ACQ >1.5: ICS decrease one step, LABA increase one step If a patient had undergone two ICS dose increments and F_{eNO} remained >29 ppb, ICS was not increased further. If still symptomatic (ACQ >1.5) formoterol 6 µg twice daily was added. For patients taking formoterol, the ICS dose could never be 0, but would be reduced to 100 µg twice daily. Patients who remained uncontrolled at maximum doses were referred to a respiratory physician.	ACQ-guided Well controlled asthma, ACQ <0.75: reduce treatment one step Partially controlled asthma, ACQ 0.75–1.50: no treatment change Uncontrolled asthma, ACQ >1.5: increase one step Those at maximum dose were referred to a respiratory physician	Steps 1–5 ICS: budesonide 0, 100, 200, 400 or 800 µg twice daily, respectively LABA: Step 1: salbutamol as required Step 2–5: formoterol 6, 12, 24 or 24 µg twice daily, respectively	Step 1: salbutamol as required Step 2: budesonide 200 µg twice daily plus salbutamol as required Step 3: budesonide 400 µg twice daily plus salbutamol as required Step 4: budesonide 400 µg and formoterol 12 µg twice daily Step 5: budesonide 800 µg twice daily and formoterol 24 µg twice daily

F_{eNO}: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s; GINA: Global Initiative for Asthma; BTS: British Thoracic Society; SIGN: Scottish Intercollegiate Guidelines Network; HFA: hydrofluoroalkanes; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate; LTRA: leukotriene receptor antagonist; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist; NHLBI: National Heart, Lung and Blood Institute; ACQ: Asthma Control Questionnaire; OCS: oral corticosteroid.

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TABLE 4 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

First author [ref.]	Methodological quality assessment: randomised controlled trials						
	Random sequence generation (selection bias)	Allocation of treatment concealed	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases (*e.g.* commercial funding)
Calhoun [13]	U	U	L	U	U	H	H
Honkoop [16]	L	L	H	H	L	L	H
Powell [26]	L	L	L	L	L	L	U
Shaw [25]	L	L	L	U	L	L	L
Smith [24]	U	U	U	U	L	L	H
Syk [14]	L	L	H	H	L	H	H

L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

Moderate and minor exacerbations

Two studies [14, 24] reported data on less severe exacerbations; however, this data was not amenable to meta-analysis due to unreported data (table 5). Both studies observed lower rates of minor/moderate asthma exacerbations in the intervention group compared with the control group. In Smith *et al.* [24], the rate was 0.36 *versus* 0.75 (p=0.24) and in Syk *et al.* [14], 0.1 *versus* 0.325 events per person year respectively (p-value not reported).

Composite of all exacerbations and failure rates

Three studies reported composite outcomes that were considered to be broadly similar and represent what may be termed "treatment failure" (table 5). In Smith *et al.* [24] and Syk *et al.* [14] this was "any major or minor exacerbation", while in Calhoun *et al.* [13] it was exacerbation or any loss of control by a variety of measures. A meta-analysis of these studies (fig. 1c) showed a statistically significant effect in favour of using *F*eNO-guided management in adults, with a rate ratio of 0.53 (95% CI 0.46–0.61; p<0.00001). However, due to high degree of heterogeneity in composite outcomes, the effect is therefore liable to high risk of bias.

ICS use

Four studies reported some data on ICS use [13, 14, 24, 25]; however, outcomes were not reported in a standardised manner (table 5). As shown in figure 1d, a meta-analysis using the standardised mean difference analysis showed a beneficial overall effect of −0.24 (95% CI −0.56–0.07) in favour of *F*eNO-guided management; however, the findings were not statistically significant (p=0.13).

Relationship between ICS use, step-up/step-down protocol and exacerbations

A *post hoc* analysis was undertaken to examine the relationship between ICS use, exacerbations and which step-up/step-down approach was used. A summary of the data is presented in table 6. Two studies that used *F*eNO levels in conjunction with symptoms showed a statistically significant decrease in ICS use in the *F*eNO-guided management groups and a nonsignificant decrease in any type of exacerbation [24, 25], thus indicating improved management overall. By contrast, the studies which managed asthma based on *F*eNO levels alone were less clear. Syk *et al.* [14] reported no change in ICS use and a nonsignificant decrease in moderate exacerbation and a nonsignificant increase in severe exacerbation, but a significant decrease in any exacerbation. Calhoun *et al.* [13] reported no difference in ICS use and exacerbations.

Other outcomes

Health-related quality of life was infrequently reported. Three studies [13, 14, 16] used versions of the Asthma Quality of Life Questionnaire to measure quality of life. Two studies showed no effect in the global score (pooled standardised mean difference: 0.00 (95%CI −0.20–0.20); p=0.96) [13, 16]. However, one study investigated domains and found a statistically significant difference in the symptoms score (p=0.041) with a between group difference in change from baseline of 0.10 in favour of *F*eNO management [14]. Asthma control was reported in all studies, but showed no statistically significant difference. Further details on other outcomes are summarised in online supplementary appendix 3.

Efficacy of FeNO in pregnant women

One study reported the efficacy of *F*eNO-guided management of asthma in pregnant women [26]. The composite outcome of all exacerbations was statistically significantly reduced in the intervention arm, with an incidence rate ratio of 0.496 per pregnancy (95% CI 0.325–0.755; p=0.001). This difference was mostly

TABLE 5 Exacerbations and inhaled corticosteroid (ICS) use in adult patients with or without fractional exhaled nitric oxide (F_{ENO})-guided management

First author [ref.]	Time of outcome	Definition of outcomes	Subjects n	Exacerbations per person year	Between group comparison	ICS use	Between group difference[#]
Smith [24]	3–12 months optimisation (exacerbation rates not reported for this period) plus 12 months titration	Minor: global daily asthma score[¶] of two on ⩾2 consecutive days	94	Intervention group[+]: 0.36 Control group[+]: 0.75	p=0.24	Final value ICS use[§] Intervention Baseline: mean 411 µg per day (95% CI 344–478) End of phase 2: mean 370 µg per day (95% CI 263–477) Control Baseline: mean 491 µg per day (95% CI 403–579) End of phase 2: mean 641 µg per day (95% CI 526–756)	Mean difference −270 µg per day (95% CI −112– −430, p=0.003)
		Major: global daily asthma score[¶] of three on ⩾2 consecutive days (or in 1 day, in the context of a minor exacerbation) Major exacerbation or medical emergency: global daily asthma score[¶] of four in 1 day		Intervention group[+]: 0.13 Control group[+]: 0.14	p=0.91		
		Any minor or major exacerbation		Intervention group: 0.49 (95% CI 0.20–0.78) Control group: 0.90 (95% CI 0.31–1.49)	−45.6% (95% CI −78.6–54.5, p=0.27) NS		
		Course of oral prednisone		Intervention group: 0.48 Control group: 0.60	p=0.60		
Shaw [25]	12 months	Course of OCS or antibiotics	118	Intervention group: 0.33 (SD 0.69) Control group: 0.42 (SD 0.79)	−21% (95% CI −57–43%, p=0.43)	Final value ICS use[f] Intervention: 557 µg Control: 895 µg	Mean difference −338 µg per day (95% CI −640– −37 µg, p= 0.028) Total used in study (AUC): 11% greater in F_{ENO} group (95% CI −15–37%)
Syk [14]	End-points analysed from visit 2 to visit 6 (2–4 weeks, 12 months)	Moderate exacerbation: need to step-up controller treatment for at least 2 days with or without clinic visit Prophylactic use before pollen season excluded	165	Intervention group: 0.1 Control group: 0.325	NR	ICS use[¶¶] Intervention Median 0 (IQR −400–400) Baseline: mean 604 (SE 370) Final value: 586 (SE 454) Control 0 (IQR −200– 200) Baseline: mean 626 (SE 391) Final value: 540 (SE 317)	0.945
		Severe exacerbation [##]: worsening requiring a course of OCS		Intervention group: 0.113 Control group: 0.0875	NS		
		Moderate or severe exacerbation		Intervention group: 0.22 Control group: 0.41	p=0.024		

Continued

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TABLE 5 Continued

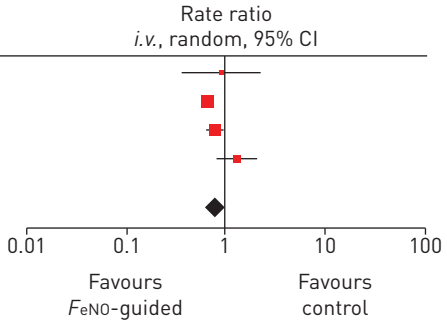
First author [ref.]	Time of outcome	Definition of outcomes	Subjects n	Exacerbations per person year	Between group comparison	ICS use	Between group difference[#]
Calhoun [13]	9 months	Exacerbation: unscheduled medical contact for increased asthma symptoms that results in the use of OCS, increased ICS or additional medication for asthma	229	Intervention group: 0.21 (97.5% CI 0.1–0.32) Control group: 0.23 (97.5% CI 0.1–0.37)	"Did not differ"	ICS use (unclear if mean over whole study or final value)[f] Intervention Mean 1617 μg·month^{-1} Control Mean 1610 μg·month^{-1}	NR
		Treatment failure defined as exacerbation or loss of control[++]		Intervention group: 0.27 (97.5% CI 0.14–0.39) Control group: 0.43 (97.5% CI 0.23–0.64)	"Were not different"		
Honkoop [16]	12 months	Severe exacerbation: course of oral prednisone, hospitalisation and/or emergency department visit	611	Intervention group: 0.19 (95% CI 0.11–0.29) Control group Strict: 0.29 (95% CI 0.17–0.40) Sufficient: 0.29 (95% CI 0.15–0.43)	Odds ratio *versus* Strict: 0.64 (95% CI 0.27–1.56) Sufficient: 0.79 (95% CI 0.32–1.92)	NR	NR
		Unscheduled healthcare utilisation: hospitalisation and/or emergency department visit		Number of visits Intervention group: 3 Controlled asthma: strict 5 Partly controlled asthma: sufficient 9	Odds ratio *versus* Strict: 0.61 (95% CI 0.14–2.58) Sufficient: 0.37 (95% CI 0.10–1.38)		

NS: nonsignificant difference; OCS: oral corticosteroid; AUC: area under curve; NR: not reported; IQR: interquartile range; PEFR: peak expiratory flow rate. [#]: Expressed as intervention minus control (negative values indicate lower F_{eNO}). [¶]: Asthma scores were as follows. 0 (stable): morning PEFR >75% of best PEFR in 14-day run-in period without deterioration in any symptom scores. 1 (mildly unstable): one or more of the following a) bronchodilator use on two or more occasions in 24 h more than the rounded mean number of occasions during the run-in period; b) increase in symptom score of 1 point or more as compared with rounded mean during run-in period; c) onset of or increase in nocturnal waking by one or more times in the previous seven nights more than rounded mean number of times during the run-in period, or morning PEFR of 61–75% without deterioration in any of the above categories. 2 (minor deterioration): morning PEFR of 61–75% of best PEFR during the run-in period and one or more criteria for an asthma score of 1; or morning PEFR of 41–60% without deterioration in any criteria for an asthma score of 1. 3 (major deterioration): morning PEFR of 41–60% of best PEFR during run-in period and one or more criteria for an asthma score of 1. 4 (major exacerbation or medical emergency): morning PEFR of 40% or less than best PEFR during run-in period regardless of symptoms, or attendance at clinician's office or emergency department because of severe asthma. [+]: Estimated off graph. [§]: Fluticasone or the equivalent. [f]: Beclomethasone diproprionate or equivalent. [##]: American Thoracic Society/European Respiratory Society Task Force Criteria 2009. [¶¶]: Budesonide equivalent. [++]: At-home measurements: 1) Pre-bronchodilator AM peak expiratory flow (PEF) of <65% of baseline on two consecutive mornings, scheduled measurements. 2) Post-bronchodilator PEF of <80% of baseline despite 60 min of rescue β-agonist treatment. 3) Post-bronchodilator PEF may be taken at any time of day, an increase in albuterol use of more than 8 puffs per 24 h over baseline use for a period of 48 h, or more than 16 puffs per 24 h for more than 48 h. In-clinic measurements: 1) Pre-bronchodilator forced expiratory volume in 1 s (FEV_1) values on two consecutive sets of spirometric determinations, measured 24–72 h apart, that are <80% of the baseline pre-bronchodilator value (baseline value for adherence period: FEV_1 value at visit 3; baseline for randomisation period: FEV_1 value at visit 4). All participants found to have an FEV_1 of <80% of baseline at any centre visit but who are not considered to meet treatment failure or exacerbation criteria must be seen again within 72 h to have FEV_1 measured. 2) Physician judgment for patient safety. 3) Patient dissatisfaction with asthma control achieved by study regimen. 4) Requirement for open-label ICSs or another (nonsystemic corticosteroid) new asthma medication (*e.g.* montelukast) without the addition of systemic corticosteroids.

a)

Study or subgroup	log (rate ratio)	SE	Weight %	Rate ratio *i.v.* random (95% CI)
Calhoun [13]	−0.09097178	0.45116134	6.3	0.91 (0.38–2.21)
Honkoop [16]	−0.41726314	0.0476771	41.1	0.66 (0.60–0.72)
Shaw [25]	−0.24116206	0.0917899	35.2	0.79 (0.66–0.94)
Syk [14]	0.25762178	0.22857143	17.4	1.29 (0.83–2.03)
Total (95% CI)			100.0	0.80 (0.63–1.02)

Heterogeneity, Tau²=0.03; Chi²=10.77, df=3 (p=0.01); I²=72%
Test for overall effect Z=1.77 (p=0.08)



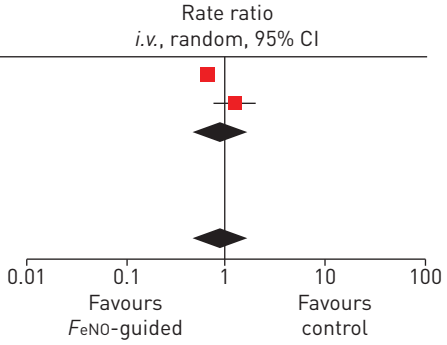
b)

Study or subgroup	log (rate ratio)	SE	Weight %	Rate ratio *i.v.* random (95% CI)
Honkoop [16]	−0.41726314	0.0476771	55.5	0.66 (0.60–0.72)
Syk [14]	0.25762178	0.22857143	44.5	1.29 (0.83–2.03)
Subtotal (95% CI)			100.0	0.89 (0.46–1.72)

Heterogeneity, Tau²=0.20; Chi²=8.35, df=1 (p=0.004); I²=88%
Test for overall effect Z=0.35 (p=0.73)

Total (95% CI)			100.0	0.89 (0.43,1.72)

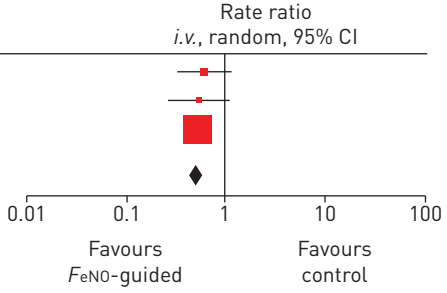
Heterogeneity, Tau²=0.20; Chi²=8.35, df=1 (p=0.004); I²=88%
Test for overall effect Z=0.35 (p=0.73)
Test for subgroup differences: Not applicable



c)

Study or subgroup	log (rate ratio)	SE	Weight %	Rate ratio *i.v.* random (95% CI)
Calhoun [13]	−0.46536325	0.2943	6.7	0.63 (0.35–1.12)
Smith [24]	−0.60798937	0.34988064	4.8	0.54 (0.27–1.08)
Syk [14]	−0.65112175	0.0811328	88.5	0.52 (0.44–0.61)
Total (95% CI)			100.0	0.53 (0.46–0.61)

Heterogeneity, Tau²=0.00; Chi²=0.38, df=2 (p=0.83); I²=0%
Test for overall effect Z=8.34 (p<0.00001)



d)

Study or subgroup	Experimental Mean±SD	Experimental Total	Control Mean±SD	Control Total	Weight %	Std. mean difference *i.v.*, random (95% CI)
Calhoun [13]	1.617±1.000	115	1.610±1.000	114	28.2	0.01 (−0.25–0.27)
Shaw [25]	557±835.7726	58	895±836.7725	60	23.8	−0.40 (−0.77– −0.04)
Smith [24]	370±360.3138	48	641±356.0468	48	21.7	−0.71 (−1.13– −0.28)
Syk [14]	586±4234.6301	87	540±2799.6682	78	26.3	0.01 (−0.29–0.32)
Total (95% CI)		306		300	100.0	−0.24 (−0.56–0.07)

Heterogeneity, Tau²=0.08; Chi²=11.11, df=3 (p=0.01); I²=73%
Test for overall effect Z=1.51 (p=0.13)

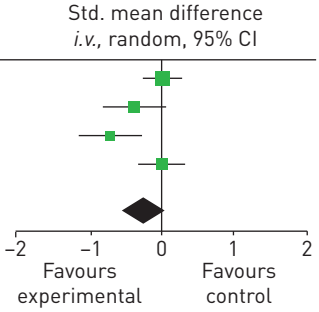


FIGURE 1 Random effects meta-analysis. a) Effects of fractional exhaled nitric oxide (*F*eNO)-guided asthma management on major/severe exacerbation rates. b) Number of severe exacerbations resulting in the use of oral corticosteroids. c) Effects of *F*eNO-guided asthma management on the composite outcome of all exacerbation and treatment failure rates. d) Effects of *F*eNO-guided asthma management on mean inhaled corticosteroids use (standardised (Std) mean difference analysis).

driven by the rate of OCS use and the rate of doctors' visits during pregnancy (table 7). Mean OCS use in the *F*eNO and control arm was 0.08 (95% CI 0.03–0.133) and 0.19 (95% CI 0.08–0.31), respectively (p=0.042). Similarly, the rate of doctors' visits was 0.26 (95% CI 0.16–0.36) in the *F*eNO arm and 0.56 (95% CI 0.40–0.72) in the control arm with a p-value of 0.002 in favour of *F*eNO management. Other components of the exacerbation outcome (hospitalisations and emergency room/labour ward visits) did not differ between groups. The change in mean value from baseline to final visit for ICS use decreased by

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TABLE 6 Relationship between inhaled corticosteroid (ICS) use, step-up/step-down protocol and exacerbations

First author [ref.]	Management plan	Severity of population	Treatment	Atopic	Exacerbation			ICS use
					Any	Major	Minor	
Smith [24]	*F*eNO + symptom-based safety protocol	Excluded severe	ICS	NR	NS decrease	NS decrease	NS decrease	SS decrease
Shaw [25]	*F*eNO + symptoms	Recent severe exacerbations excluded	ICS, LTRA, bronchodilator	66%	NR	NS decrease	NR	SS decrease
Syk [14]	*F*eNO only	Mild to moderate	ICS, LTRA	100%	SS decrease	NS increase	NS decrease (moderate)	No change
Calhoun [13]	*F*eNO only	Mild to moderate	ICS	86%	No change	No change	NR	No change
Honkoop [16]	*F*eNO + symptoms	Excluded those taking OCS every day/every other day	ICS, SABA, LABA, LTRA, OCS	54%	NR	NS decrease	NR	NR

*F*eNO: fractional exhaled nitric oxide; NR: not reported; NS: nonsignificant; SS: statistically significant; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; SABA: short-acting β_2-agonist; LABA: long-acting β_2-agonist.

210 μg·day^{-1} in the intervention arm and increased by 50 μg·day^{-1} in the control arm. The difference was statistically significant in favour of *F*eNO management (p=0.043). However, overall more patients received ICS (68% *versus* 42%) in the *F*eNO group than in the control group by the end of the study. Other outcomes are summarised in table 7.

Discussion

In this systematic review, six RCTs were identified that assessed the use of *F*eNO for the management of asthma in adults [13, 14, 16, 24–26]. In general, using exploratory meta-analysis, a fall in exacerbation rates per person year were observed, but none were statistically significant apart from the composite of all exacerbations and failure rates. However, the findings should be interpreted with caution due to the high degree of heterogeneity in the outcome definition. The effects on ICS use were heterogeneous, although the direction of the effect was towards a decrease in ICS use. The effect on healthcare utilisation was not statistically significant; however, as this outcome was only reported in one low quality study [16], to base any conclusion on this could be misleading. The use of *F*eNO to guide asthma management in pregnant women in the second trimester appears to be as effective, if not more so, than in other adults [26], and appears to reduce exacerbations and ICS use, but by the end of the study more patients in *F*eNO group had received ICS. The differences in outcome between studies may have occurred due to some step-up/step-down protocols being better at decreasing ICS use than others, or may be due to the characteristics of the study populations. Other potential factors as to why the *F*eNO monitoring studies have been predominately negative could be due to the difference in severity of asthma at baseline, different treatment strategies used (*i.e.* some studies controlled only ICS while some also controlled other medications), differences in the number and points of *F*eNO cut-off used, and also the comparator groups did not all use the same algorithm.

There are at least two previous systematic reviews on the effectiveness of *F*eNO monitoring to guide management [9, 11]. Petsky *et al.* [9] compared adjustments of asthma therapy based on *F*eNO with conventional methods (typically clinical symptoms and spirometry). The review suggested some benefits associated with *F*eNO for several outcomes, in particular the number of subjects with >1 exacerbation, exacerbation rates, FEV1 % predicted at final visit and geometric change in *F*eNO from baseline; however, none of these results were statistically conclusive. *F*eNO appeared to have some beneficial effect on symptom score (mean difference: −0.14, 95% CI −0.42–0.14) and lowered ICS dose (mean difference: −450.03 μg, 95% CI −676.73–−223.34 μg). Furthermore, there was substantial clinical heterogeneity among the study cohorts, with no two studies using exactly the same step-up/step-down protocols. There is some agreement between the review by Petsky *et al.* [9] and our own review, especially relating to the lack of statistically significant effects in most outcomes. The strength of our review lies in the inclusion of subsequently published studies (Calhoun *et al.* [13], Syk *et al.* [14] and Honkoop *et al.* [16]), the focus on exacerbation rates rather than number of people with an exacerbation, and the prior separation of

TABLE 7 Pregnant women: all outcomes

Time of outcome	Definition of outcomes	Intervention	Control	Between group comparison
Exacerbations[#]	Exacerbations: an unscheduled visit to a doctor, presentation to the emergency room or admission to hospital, or when OCS used Events separated by 7 days or more were counted as a second event	0.288 per pregnancy (mean±SD study time 17.8±5.5 weeks)	0.615 per pregnancy (mean study time 18.8±3.8 weeks)	Incidence rate ratio 0.496 (95% CI 0.325–0.755), p=0.001
	Mean (95% CI) OCS use	0.08 (0.03–0.133)	0.19 (0.08–0.31)	p=0.042
	Mean (95% CI) hospitalisations	0 (0–0)	0.03 (−0.004–0.06)	p=1.0
	Mean (95% CI) emergency room/labour ward visits	0.04 (0.001–0.07)	0.02 (−0.01–0.04)	p=0.399
	Mean (95% CI) unplanned or unscheduled doctors' visits	0.26 (0.16–0.36)	0.56 (0.40–0.72)	p=0.002
ICS use	Difference in means (from baseline to last visit) (read off graph):	−210 μg·day^{-1}	50 μg·day^{-1}	p=0.043
	Median (IQR) BDP equivalent ICS dose (μg·day^{-1})	200 (0–400)	0 (0–800)	p=0.079
	Users	76 (68.5%) out of 111	46 (42.2%) out of 109	p<0.0001
Other outcomes	Median (IQR) HRQoL			
	SF-12 physical summary (low 0, high 100):	47.7 (40.8–52.0)	46.9 (38.2–51.8)	p=0.89
	SF-12 mental summary (low 0, high 100):	56.9 (50.2–59.3)	54.2 (46.1–57.6)	p=0.037
	AQLQ-M: total score (good 0, poor 10):	0.75 (0.38–1.25)	0.81 (0.38–1.63)	p=0.54
	Asthma control: mean±SD ACQ	0.56±0.67	0.72±0.80	p=0.046
	Median (IQR) β_2-agonist use in past week	0 (0–3)	1 (0–5)	p=0.024
	LABA users	45 (40.5%) out of 111	19 (17.4%) out of 109	p<0.0001
	Adverse events, mortality, compliance and test failure rates	NR	NR	NR

OCS: oral corticosteroids; IQR: interquartile range; BDP: beclomethasone diproprionate; ICS: inhaled corticosteroid; HRQoL: health-related quality of life; SF-12: short form 12; AQLQ-M: Asthma Quality of Life Questionnaire-Marks; ACQ: Asthma Control Questionnaire; LABA: long-acting β_2-agonist; NR: not reported. [#]: time of outcome was monthly until birth (maximum ~30 weeks). Information from [26].

pregnant women into a different subgroup. The second review by DONOHUE and JAIN [11] updated the meta-analyses of the number of patients with >1 exacerbation and exacerbation rates from the aforementioned Cochrane review [9], and included a study in pregnant women [26]. Inclusion of this study resulted in improvements on all measures of exacerbations (mean difference: −0.27, 95% CI −0.42–−0.12), and the relative rate of asthma exacerbations (relative rate: 0.57, 95% CI 0.41–0.80). However, since it is known that pregnancy can substantially affect the course of asthma [12], it was arguably inappropriate to include the cohort of pregnant women in a meta-analysis of adults with asthma.

One of the putative benefits of using *F*eNO for the management of asthma is the identification of patients for whom increased ICS use will not improve control. These patients are likely to present with symptoms, which would indicate an increase in pharmaceutical management under standard clinical guidelines, and under most of the *F*eNO protocols that have been studied to date, whereas they may be better treated with other asthma control medications. A key limitation is therefore the paucity of studies that allowed step-down of ICS to be performed on the basis of low *F*eNO values alone. Only two studies [13, 14] and the study in pregnant women [26] included such a strategy, and only POWELL *et al.* [26] made provision for adjusting other treatments which may offer superior control in these patients in response to their reported symptomatology. We did not plan or perform a sensitivity analysis of this data, but did present a rudimentary analysis of the relationship between ICS use, management protocols and exacerbations (table 6). It is interesting to note that the two studies that managed patients on the basis of *F*eNO only (SYK *et al.* [14] and CALHOUN *et al.* [13]) did not report any change in ICS use, which is perhaps contrary to expectations, or in severe exacerbations. However, SYK *et al.* [14] did report a fall in exacerbations overall. In comparison, the two studies that managed patients on the basis of *F*eNO and symptoms (SMITH *et al.* [24] and SHAW *et al.* [25]) reported a statistically significant decrease in ICS use and a nonsignificant decrease in exacerbations. This perhaps indicates a shift in treatment patterns, with better targeting of

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treatment with the addition of *F*eNO to the patients who will benefit most. In addition, although there was no significant difference in compliance with treatment between the *F*eNO management and control group, there is a potential that *F*eNO may help improve compliance with ICS use.

There are a number of limitations to our review which warrant caution in its interpretation to clinical practice. The evidence from the included studies are of low quality and there is significant heterogeneity in all aspects of study design across the studies, including patient characteristics, outcome definitions, *F*eNO cut-off points and in management protocols, hence an exploratory meta-analysis was used to overcome these differences. In addition, the management plan used in some studies did not reflect real life practice, for example in the study by Smith *et al.* [24], long-acting β_2-agonist (LABA) was not used and patients underwent a step-down therapy approach in the pre-study phase. It is noteworthy that LABA in combination with ICS are key steps in asthma management. The equivalence of devices is assumed and this may not hold true in practice. As such, *F*eNO cut-off values as reported in the primary research may not be applicable to measurements using other devices. Smoking affects *F*eNO levels and majority of the patients in this review were nonsmokers, hence it is not clear if the results can be generalised to the smoking population. Also, the average age of patients in this review was around 40 years old. However, the majority of asthma deaths occur in older people with severe disease. All the included studies recruited patients that were stable during the run-in period and excluded the more severe/difficult patients with recent hospital admissions. So, by definition, some of the real life "difficult" patients, who require more help, were excluded. Finally, the criteria used for the diagnosis of asthma across the included studies varied with limited data and as recent studies have reported the potential of overdiagnosis of asthma, this may have implications for the results. It is important to note that these limitations are principally sourced in the evidence base, rather than the methods used to interrogate and evaluate it. One should also bear in mind that the addition of *F*eNO to the current management strategy will require change in organisation and to the philosophy of care in self-management.

Conclusion

*F*eNO guided management showed no statistically significant benefit in terms of severe exacerbations or ICS use, but showed a statistically significant reduction in exacerbations of any severity. Due to heterogeneity in the studies it was not possible to draw any firm conclusions as to which management protocol or cut-off points offer the best efficacy. Further research is required to investigate the best way to use *F*eNO in the management of asthma, which management protocol and cut-offs to use; to establish which patient groups are likely to benefit from *F*eNO monitoring, *e.g.* individuals with atopy, frequent exacerbations or those with poor adherence; and how treatment effect will progress over time. Larger, well designed RCT studies, taking into account issues such as severity as defined by previous exacerbations, blinding and approximating to routine care are warranted to clearly define the role of *F*eNO in clinical practice.

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