The Use of Exhaled Nitric Oxide to Guide Asthma Management:
A Randomised Controlled Trial

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Rationale

Current asthma guidelines recommend adjusting anti-inflammatory treatment on the basis of the results of lung function tests and symptom assessment, neither of which are closely associated with airway inflammation.

Objectives

We tested the hypothesis that titrating corticosteroid dose using the concentration of exhaled nitric oxide in exhaled breath (FE\textsubscript{NO}) results in fewer asthma exacerbations and more efficient use of corticosteroids, when compared to traditional management.

Methods

118 participants with a primary care diagnosis of asthma were randomised to a single blind trial of corticosteroid therapy based on either FE\textsubscript{NO} measurements (n = 58) or British Thoracic Society guidelines (n = 60). Participants were assessed monthly for 4 months and then two monthly for a further 8 months. The primary outcome was the number of severe asthma exacerbations. Analyses were by intention to treat.

Measurements and Main Results

The estimated mean (SD) exacerbation frequency was 0.33/patient/year (0.69) in the FE\textsubscript{NO} group and 0.42 (0.79) in the control group (mean difference -21% [95% CI -57% to 43%] p=0.43). Overall the FE\textsubscript{NO} group used 11% more inhaled corticosteroid ([95% CI -17% to 42%] p=0.40), although the final daily dose of inhaled corticosteroid was lower in the FE\textsubscript{NO} group (557µg vs. 895µg, mean difference 338µg [95% CI -640 to -37] p=0.028).
Conclusion

An asthma treatment strategy based on the measurement of exhaled nitric oxide did not result in a large reduction in asthma exacerbations or in the total amount of inhaled corticosteroid therapy used over 12 months, when compared with current asthma guidelines.
**Introduction**

Asthma is defined and characterised by the presence of symptoms associated with variable airflow obstruction, airway inflammation and airway hyperresponsiveness\(^1\). It is a common disease which is responsible for significant morbidity, mortality and health care cost\(^2\). Current guidelines recommend that decisions about treatment are based on assessment of symptoms and airflow obstruction. However, there is no clear relationship between symptom control, variable airflow obstruction and the extent of eosinophilic airway inflammation\(^3;4\) and a response to corticosteroids is most closely associated with the presence of eosinophilic airway inflammation\(^5\). There is also evidence that management with the additional aim of decreasing eosinophilic airway inflammation reduces exacerbation frequency in patients managed in secondary care, and that a sputum eosinophilia is a marker of preventable, corticosteroid responsive asthma exacerbations\(^6\). In the U.K. 80% of patients with asthma are managed in primary care\(^7\); assessment of eosinophilic airway inflammation using induced sputum is not applicable in this setting\(^6\).

Recently the concentration of nitric oxide present in exhaled breath (FE\(_{\text{NO}}\)) has been evaluated as a tool for assessing asthma\(^8\). FE\(_{\text{NO}}\) is elevated in patients with asthma\(^9;10\), is reduced by treatment with inhaled corticosteroids\(^10\) and correlates with eosinophilic airway inflammation measured using bronchial biopsies and induced sputum\(^11;12\). It is particularly applicable for monitoring asthma in primary care as the test is easy to perform\(^13\), it provides an immediate result, and inexpensive portable monitors are now available. Two recent studies have investigated the use of FE\(_{\text{NO}}\) to guide treatment in asthma\(^14;15\). Neither study showed an improvement in exacerbation frequency although in one study the daily dose of inhaled steroids was lower\(^14\).
Our aim was to test the hypothesis that the use of $\text{FE}_\text{NO}$ for titrating corticosteroid dose results in fewer exacerbations and more efficient use of corticosteroid therapy. We designed a single-blind randomised controlled trial comparing exacerbation frequency and corticosteroid dosage in patients whose asthma management was based on measurements of $\text{FE}_\text{NO}$ to one where management was based on the British Thoracic Society and Scottish Intercollegiate Guidelines Network treatment guidelines$^{16}$. Results from this work have previously been published as an abstract$^{17}$.

**Setting and Participants**

Participants were identified from registers held in General Practices around Leicester. All participants were aged over 18 and had a diagnosis of asthma recorded in their GP notes. Participants were eligible if they had received at least one prescription for any anti-asthma medication in the last 12 months. The study was restricted to current non-smokers with a past smoking history of less than 10 pack years. Participants were also excluded if they were considered by their physician to be poorly compliant or had had a severe asthma exacerbation, requiring a course of prednisolone, within 4 weeks of study entry. All suitable participants on the registers who responded to an invitation from their GP to be contacted by the research team were invited to participate in the study. Ethical approval for the study was given by ethics committees from both the University Hospitals of Leicester and the Leicester Primary Research Care Alliance; all participants gave written informed consent.

**Clinical Methods**

Participants attended Glenfield Hospital for tests to characterise their asthma. Tests were performed in the following order and at the same time of day for each patient: exhaled nitric
oxide levels measured at a flow of 50mL/sec, forced expiratory volume (FEV\textsubscript{1}) and forced
vital capacity (FVC), methacholine challenge test to determine the concentration of
methacholine required to provoke a 20% fall in the FEV\textsubscript{1}, induced sputum analysis and skin
prick tests to common aeroallergens. Participants were seen 2 weeks later and then every
month for 4 months followed by every 2 months for a further 8 months in order to be
consistent with our earlier study of inflammation guided management\textsuperscript{6}. Each visit occurred at
the same time of day and consisted of assessment of exhaled nitric oxide, spirometry and
post bronchodilator FEV\textsubscript{1}, 20 minutes after 400µg salbutamol at the end of every visit (Figure
1). Peak flow and symptom diaries were analysed and compliance assessed by monitoring
adherence to script collection. Participants were issued with self management plans based on
their best baseline peak flow from the first 2 weeks of the study; if their peak flow fell to less
than 70% of their best for 48 hours during the study, or their asthma deteriorated, they
were asked to attend hospital where they were assessed by a physician (MB). At the 6 and
12 month visit induced sputum and methacholine challenge testing were also performed. Full
details of the measurements made are provided in the on-line supplement.

**Intervention**

After the first visit participants were randomly allocated to receive treatment either on the
basis of their F\textsubscript{E}NO measurements (F\textsubscript{E}NO group) or according to a conventional stepwise
asthma management plan (control group)\textsuperscript{16}. Randomisation was done by an independent
individual (CB) with the method of minimisation\textsuperscript{18}, and was stratified by the baseline sputum
eosinophil count, F\textsubscript{E}NO and rescue steroid courses in the last year. Participants were seen
monthly for the first 4 months and 2 monthly thereafter (Figure 1); all visits were at the
same time of day. At each visit the patient’s asthma control was determined using the
validated Juniper asthma control questionnaire which scores asthma control from 0-6; a score of greater than 1.57 was used to identify poorly controlled asthma. In the control group treatment was doubled if the score was >1.57, and treatment was halved if the score was <1.57 for 2 consecutive months (Figure 1, online supplement). In the FE\textsubscript{NO} group treatment was adjusted following a set protocol according to both the FE\textsubscript{NO} and Juniper scores (Figure 2, online supplement). If the FE\textsubscript{NO} was greater than 26ppb inhaled corticosteroid treatment was increased, if it was less than 16 ppb or less than 26ppb on 2 consecutive occasions it was decreased. Bronchodilator therapy was increased if symptoms were uncontrolled, despite a FE\textsubscript{NO} of <26ppb. We chose these cut offs as they have been shown to best identify a sputum eosinophil count of >3% and <1% respectively, after correction for expiratory flow. Assessment of asthma control was made per protocol by investigators who were unaware of the participants’ randomisation status (BH/SM/MS/HP). At each visit two different treatment decisions, one for each randomisation group, were made by an independent physician who was also unaware of the randomisation status (RG/IP). The correct treatment decision, according to the participants’ group, was communicated to the patient by a separate unblinded physician (DS).

**Safety Measure**

As there was evidence before study commencement that a high FE\textsubscript{NO} would not always reflect a high differential sputum eosinophil count, we determined \textit{a priori} that patients in the FE\textsubscript{NO} group who had their anti-inflammatory treatment increased to the equivalent dose 2000µg beclomethasone dipropionate (BDP) per day, and whose FE\textsubscript{NO} was still greater than 26ppb, and had not fallen to 60% of baseline, would have their differential sputum eosinophil count checked. If there was no eosinophilic airway inflammation present,
treatment was reduced in a stepwise fashion, unless the $\text{FeNO}$ increased by greater than 60% from baseline. An inhaled corticosteroid dose of 2000µg BDP was chosen as this is the normal point for referral from primary care for secondary care evaluation.

An asthma exacerbation was defined *a priori* as an episode of increasing asthma symptoms requiring a course of oral steroids or antibiotics; participants were asked to contact the research nurses if their asthma deteriorated. Participants were assessed and treated according to the BTS guidelines by a physician (MB) not involved in the regular treatment decisions and blinded to the participants’ randomisation status. At the end of the study participants were asked to record which group they thought they had been assigned to as an assessment of the success of blinding.

**Analysis**

We estimated that we needed 53 participants in each group to give 80% power to detect a 50% reduction in the rate of asthma exacerbations, based on a Poisson regression analysis and a two-sided test at the 5% level. Our power calculation was based on findings from the FACET study which found an exacerbation frequencies of 0.91/patient/year and our own audit data suggesting that exacerbation frequency approximates to a Poisson distribution. We confirmed goodness of fit to a Poisson distribution prior to doing the analysis. If participants withdrew from the study we analysed their data by intention to treat; the last value recorded was carried forward for inhaled corticosteroid dose and $\text{FeNO}$ reading, and for methacholine responsiveness and sputum eosinophils, the mean of the previous values was used. $\text{FeNO}$ was log transformed, in order to assume a normal distribution, and expressed as a geometric mean; it was compared over the 12 months as area under the curve using an
independent t-test. Steroid dose (expressed as equivalent dose to beclomethasone dipropionate (BDP)$^6$ was also compared over the 12 months of the study as area under the curve using an independent t-test. Differential sputum eosinophil count and methacholine $\text{PC}_{20}$ were log transformed in order to assume a normal distribution, and their changes at 6 and 12 months from baseline were compared using an independent t-test. All data was analysed using SPSS for Windows (version 12) and Intercooled Stata for Windows (version 7).

**Results**

900 participants were contacted by their own GP. Of these, 146 participants declined the invitation and 636 failed to respond (Figure 2). We recruited 119 participants between January 2004 and December 2004; one patient could not perform the measurement of exhaled nitric oxide; 58 were allocated to the $\text{FE}_{\text{NO}}$ group and 60 to the control group. 6 participants withdrew from the $\text{FE}_{\text{NO}}$ group and 9 participants from the control group. None of the participants withdrew because of poorly controlled asthma. The two treatment groups were well matched at baseline for demographic and clinical features. (Table 1). Measurement of exhaled nitric oxide was successful on every occasion. Assessed as area under the curve over the 12 months of the study, the $\text{FE}_{\text{NO}}$ was 24% lower ([95% CI -8% to 55%] $p=0.14$) in the $\text{FE}_{\text{NO}}$ group when compared to control group. There was no difference in the Juniper asthma control score, peak expiratory flow readings and $\text{FEV}_1$ between the groups over the duration of the study. (Figure 3). Nine participants in the $\text{FE}_{\text{NO}}$ group needed a reassessment of management goals because of corticosteroid resistant persistent elevation of $\text{FE}_{\text{NO}}$ which was not reflective of eosinophilic airway inflammation.
There were 18 exacerbations in 12 participants in the FE\(_{\text{NO}}\) group and 26 exacerbations in 19 participants in the control group. The rate of asthma exacerbation experienced by the FE\(_{\text{NO}}\) group was 0.33/patient/year (SD 0.69) compared with 0.42 (SD 0.79) in the control group (mean difference -21% [95% CI -57% to 43%] \(p=0.43\); (Figure 4). In the 9 patients in the FE\(_{\text{NO}}\) group with discordant nitric oxide and sputum eosinophil counts the rate of asthma exacerbation experienced was 0.11/patient/year (S.D. 0.3), whereas in the 49 patients with concordant markers of airway inflammation in the FE\(_{\text{NO}}\) group, the exacerbation rate was 0.25/patient/year (S.D. 0.69). The total amount of inhaled corticosteroid used during the study was 11% greater ([95% CI -15% to 37%] \(p=0.40\)) in the FE\(_{\text{NO}}\) group compared with the control group. However, the final daily dose of inhaled corticosteroid was significantly lower in the FE\(_{\text{NO}}\) group compared to the control group (557µg vs. 895µg, (mean difference 338µg, [95% CI -640 to -37]; \(p=0.028\); (Figure 3). At 6 months there was a 0.5 doubling dose improvement in the methacholine PC\(_{20}\) in the FE\(_{\text{NO}}\) group and a 0.7 doubling dose worsening in the control group (mean difference 1.14 [95% CI -0.09 to 2.36] \(p=0.07\)). At 12 months there was a 0.2 and 0.6 doubling dose improvement in the PC\(_{20}\) in the FE\(_{\text{NO}}\) group and control group respectively (mean difference 0.34 [95% CI -1.37 to 0.69] \(p=0.51\)). The differential sputum eosinophil count had reduced at 6 months by 1.6 fold and 1.4 fold in the FE\(_{\text{NO}}\) group and control group respectively \((p=0.43)\) and at 12 months the eosinophil count had increased by 1.01 fold and 1.31 fold in the FE\(_{\text{NO}}\) group and control group respectively \((p=0.48)\). Overall 5 patients (8%) had long acting \(\beta_2\) agonists started in the FE\(_{\text{NO}}\) group and 7 (12%) patients had them started in the control group.

In a separate subgroup analysis, both groups were split into subjects with and without evidence of variable airflow obstruction, defined as one or more of the following: PC\(_{20}\)
<8mg/ml at the first visit; peak expiratory flow amplitude percent of mean >20%; improvement in FEV$_1$ >15% following 400µg salbutamol at the second visit. The rates of exacerbation were lower in the subgroups without variable airflow obstruction within both the FE$_{NO}$ group (n=44) and control group (n=39) respectively, but the differences were not significant. In the FE$_{NO}$ group exacerbation rates were 0.36 compared to 0.23 exacerbations/patient/year for participants with and without variable airflow obstruction, respectively (p=0.57); in the control group the exacerbation rates were 0.49 and 0.29 exacerbations/patient/year for participants with and without variable airflow obstruction, respectively (p=0.35). There was no significant difference in exacerbation rates in subjects with variable airflow obstruction between the FE$_{NO}$ group and control group (p=0.44).

Baseline log FE$_{NO}$ correlated with log sputum eosinophil count ($r^2=0.455$, p<0.001; (Figure 5). A FE$_{NO}$ of <26ppb was associated with a differential sputum eosinophil count of <3% for 85% of all visits when both were measured. However, on over half the occasions when both were measured, an FE$_{NO}$ of >26ppb was associated with a sputum eosinophil count of <3%. In participants with sputum eosinophils >3% and FE$_{NO}$ of >26ppb exacerbation frequency was 0.38 versus 0.67 exacerbations/patient/year in the FE$_{NO}$ group compared with the control group respectively. In participants with sputum eosinophils <3% and a FE$_{NO}$ of >26ppb exacerbation frequency was 0.09 versus 0 exacerbations/patient/year in the FE$_{NO}$ group compared with the control group respectively. The demographic details of each group were not different. The assessment of blinding revealed that 49% of participants were not sure which group they had been assigned to, 33% correctly identified their group and 18% incorrectly identified their group.
**Discussion**

Our study was designed to evaluate the use of $\text{FE}_{\text{NO}}$ to guide asthma management in primary care, a setting where the technique is likely to be particularly applicable. The use of $\text{FE}_{\text{NO}}$ measurements to guide treatment decisions did not result in lower exacerbation frequency or in a lower maintenance dose of inhaled corticosteroid when compared to traditional asthma management. Although participants in the $\text{FE}_{\text{NO}}$ group finished the study on a significantly lower dose of inhaled corticosteroid, use of inhaled corticosteroid over the 12 months of the study was not different between the groups.

Participants randomised to both groups experienced a considerably lower exacerbation frequency compared to that initially estimated and to that experienced over the previous year. This improvement was not seen in the control arm of an earlier study in participants with more severe asthma recruited from secondary care\(^6\), suggesting that the improvement in asthma control was because of more intensive monitoring in a secondary care setting. As a result of this improvement, our study was underpowered to exclude a 50% reduction in exacerbation frequency.

Our findings are consistent with those of two recent studies\(^{14}\), neither of which found a significant reduction in exacerbation frequency with $\text{FE}_{\text{NO}}$ directed management. The study of Smith et al found that $\text{FE}_{\text{NO}}$ directed management was associated with a significant decrease in inhaled corticosteroid dose\(^{14}\); the number of prednisolone courses administered was 0.48 and 0.6/patient/year in the $\text{FE}_{\text{NO}}$ and control groups respectively\(^{14}\). Pijnenburg et al. reported an improvement in airway hyperresponsiveness, but no reduction in corticosteroid dosage or
exacerbation rates using F_{ENO} directed management in a population of 85 children\textsuperscript{15}; 7 children experienced an exacerbation (defined as course of oral prednisolone) in the F_{ENO} group and 10 in the control group respectively; both groups experienced a significant increase in inhaled corticosteroid dose during the study. Comparison across studies is not straightforward as there were important differences in management protocols and F_{ENO} target ranges. In particular use of long acting β agonists, which has been associated with a lower exacerbation frequency, was not allowed in the study by Smith et al\textsuperscript{14}. However, the effect of F_{ENO} guided management on exacerbation rates is consistent across studies. This increases our confidence that a large effect of F_{ENO} guided management on exacerbation frequency is unlikely. We cannot exclude a smaller albeit clinically relevant effect. Longer and larger studies will be required to do this.

We chose our F_{ENO} cut off values on the basis of earlier work identifying them as the best indicators of the presence or absence of a raised sputum eosinophil count\textsuperscript{21} a measure that has been consistently shown to be useful in monitoring asthma\textsuperscript{6,25}. The fact that F_{ENO} guided management was most effective in participants where F_{ENO} and sputum eosinophil counts were concordant is consistent with the view that F_{ENO} acts as a marker of eosinophilic airway inflammation. The absence of effect of F_{ENO} guided management on exacerbation frequency makes it unlikely that F_{ENO} is identifying additional aspects of the inflammatory response that are important in the pathogenesis of preventable exacerbations of asthma; it also implies that F_{ENO} is an imperfect marker of eosinophilic airway inflammation. A post hoc analysis indicated that our cut off for increasing inhaled corticosteroid dose was a sensitive, but not specific, marker of eosinophilic inflammation. This meant that in a significant proportion of participants inhaled corticosteroid therapy was increased in the absence of eosinophilic
airway inflammation; exacerbation frequency in these participants was low whether randomised to the F\textsubscript{ENO} or control groups. Our study had a built in safety measure where participants whose F\textsubscript{ENO} remained raised despite a daily dose of 2000µg BDP equivalent had a more detailed evaluation with reference to previously measured induced sputum eosinophil counts. We did this because we reasoned that clinicians would be uncomfortable with increasing therapy beyond this level without specialist review and because current guidelines recommend a review in participants whose asthma is uncontrolled at BTS treatment step 4\textsuperscript{16}. As a result of this evaluation, the goals of management were changed in a significant proportion (16%) of participants randomised to F\textsubscript{ENO} guided management; this is the most likely explanation for the initial increase and then decrease in the inhaled corticosteroid dose seen in the F\textsubscript{ENO} group. The presence of a significant proportion of participants with an elevated F\textsubscript{ENO} associated with a normal sputum eosinophil count who have a good prognosis is an important limitation of the technique. Our study did not identify and obvious clinical characteristics associated with this pattern of inflammatory markers; further work is required to investigate this. Low F\textsubscript{ENO} values were reliably associated with absence of eosinophilic inflammation, supporting suggestions\textsuperscript{26} that a strategy of using of F\textsubscript{ENO} to guide reduction of inhaled corticosteroid dose might be more effective than the strategy adopted by us.

Our study has several limitations. Firstly, it was not possible to design this study in a double-blinded method. However, the potential for bias was reduced by ensuring that the subjects were blind to their randomisation status, treatment decisions were made in strict accordance with the protocol and rescue oral corticosteroids or antibiotics were started by a physician who was also unaware of the participants’ randomisation status. Secondly, our study could be criticised as we recruited participants with a clinical diagnosis of asthma. It is possible that
a clearer reduction in exacerbations would have been seen in participants recruited on the basis of the results of physiological or pathological tests. However, the diagnosis of asthma in the UK remains a largely clinical one\textsuperscript{16} and we were keen to recruit participants who were representative of those currently seen in primary care. Furthermore, a subgroup analysis on participants with objective evidence of variable airflow obstruction did not show a significant reduction in exacerbation rates within the FE\textsubscript{NO} group. Thirdly, it is possible that more frequent monitoring of FE\textsubscript{NO} might have led to a better outcome. Future studies should investigate whether this is the case and whether a protocol involving more frequent monitoring of FE\textsubscript{NO} is achievable in primary care. Finally, there is a concern about the generalisability of our findings since our population had more severe asthma than that seen previously in a primary care population\textsuperscript{27}. This may be because recruitment of participants was constrained by limitations imposed by the ethics committees meaning that participants were particularly committed, as they had to respond to both an initial invitation from their primary care practitioner to be contacted and then an invitation to participate. This factor is unlikely to be responsible for the absence of effect of FE\textsubscript{NO} guided management as there is evidence that management guided by markers of eosinophilic inflammation works best in participants with more severe asthma, and in those in whom long acting $\beta_2$ agonists are used\textsuperscript{24}. However, we cannot discount the possibility that we recruited a population who were particularly aware of their asthma symptoms and who responded particularly well to traditional management.

In conclusion we have found that a management strategy using FE\textsubscript{NO} to guide asthma treatment is feasible in participants with asthma managed in primary care, but does not lead
to a large reduction in either asthma exacerbations or inhaled corticosteroid use when compared to the current treatment strategy.

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This study was funded by a grant from Asthma UK. The study sponsor had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

**Acknowledgments**

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0 weeks (randomisation)  
FEV₁, FENO, JACS, PC_{20}, Sputum, SPT  

2 weeks  
FEV₁, FENO, JACS  

1 month  
FEV₁, FENO, JACS  

2 months  
FEV₁, FENO, JACS  

3 months  
FEV₁, FENO, JACS  

4 months  
FEV₁, FENO, JACS  

6 months  
FEV₁, FENO, JACS, PC_{20}, Sputum  

8 months  
FEV₁, FENO, JACS  

10 months  
FEV₁, FENO, JACS  

12 months  
FEV₁, FENO, JACS, PC_{20}, Sputum
Figure 1 Study Design

$\text{FE}_{\text{NO}}$ - Fraction of exhaled nitric oxide at 50ml/sec

SPT - Skin prick tests

$\text{PC}_{20}$ - Methacholine challenge test

Sputum - Differential sputum eosinophil count

JACS - Juniper asthma control score
900 patients contacted

119 patients recruited

1 patient could not perform FeNO test

118 patients randomised

FEV1, FeNO, JACS, PC20, Sputum, SPT

58 FeNO group

6 withdrew during follow up;
1 intercurrent illness
2 moved away
3 changed mind

52 completed 12 month follow up

60 Control group

9 withdrew during follow up;
2 intercurrent illness
2 moved away
4 changed mind
1 pregnancy

51 completed 12 month follow up

781 declined, or failed to respond to initial letter from GP or contact letter from research team
Figure 2 Consort profile

JACS- Juniper asthma control questionnaire

Sputum- Induced sputum differential cell count

SPT- Skin prick tests

PC$_{20}$ - Methacholine challenge test
<table>
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<th></th>
<th>FE\textsubscript{NO} Group</th>
<th>Control Group</th>
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<tr>
<td><strong>Number</strong></td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td><strong>BTS Step</strong></td>
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</tr>
<tr>
<td>Step 1</td>
<td>9 (16%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Step 2</td>
<td>24 (41%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Step 3</td>
<td>9 (16%)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Step 4</td>
<td>14 (24%)</td>
<td>14 (23%)</td>
</tr>
<tr>
<td>Step 5</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
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<td><strong>Demographic</strong></td>
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<tr>
<td>Female</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Age, years#</td>
<td>50 (20-75)</td>
<td>52 (24-81)</td>
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<tr>
<td>BMI, kg/m^2</td>
<td>27.5 (5.02)</td>
<td>28.1 (5.43)</td>
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<tr>
<td>% former smokers</td>
<td>22</td>
<td>25</td>
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<tr>
<td>Oral steroid courses in last year/patient</td>
<td>1.2 (2.0)</td>
<td>1.3 (1.8)</td>
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<td>Daily dose inhaled corticosteroid, µg</td>
<td>697 (708)</td>
<td>652 (533)</td>
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<td><strong>Clinical</strong></td>
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<tr>
<td>Atopy %</td>
<td>62</td>
<td>70</td>
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<tr>
<td>Family history of asthma (%)</td>
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<td>Rhinitis (%)</td>
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<td>Nasal Polyps (%)</td>
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<td>8</td>
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<tr>
<td>FEV\textsubscript{1}, litres</td>
<td>2.5 (0.92)</td>
<td>2.57 (0.99)</td>
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<td>FEV\textsubscript{1} as % predicted</td>
<td>81.4 (20.9)</td>
<td>84.9 (20.1)</td>
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<td>FEV\textsubscript{1}/FVC</td>
<td>71 (10.7)</td>
<td>72 (9.9)</td>
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<td>% change post salbutamol</td>
<td>6.2 (9.4)</td>
<td>5.4 (8.6)</td>
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<td>Peak expiratory flow amplitude % mean</td>
<td>23.9 (17.1)</td>
<td>18.7 (10.4)</td>
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<td>Sputum eosinophil count, %*</td>
<td>1.3 (0.3, 5.7)</td>
<td>1.7 (0.3, 9.8)</td>
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<td>Sputum neutrophil count, %</td>
<td>65.7 (27.7)</td>
<td>62.0 (21.6)</td>
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<td>Total cell count*(10\textsuperscript{6}/ml)</td>
<td>1.4 (0.3, 7.0)</td>
<td>1.4 (0.3, 6.3)</td>
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<td>Methacholine PC\textsubscript{20}* (mg/ml)</td>
<td>1.4 (0.1, 16.0)</td>
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<td>Juniper asthma control score</td>
<td>1.32 (0.65)</td>
<td>1.26 (0.75)</td>
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<td>FE\textsubscript{NO} ppb*</td>
<td>29.2 (14.0, 61.0)</td>
<td>31.2 (13.3, 73.1)</td>
</tr>
</tbody>
</table>
Table 1 Baseline Demographics by Group
Figures are mean (SD) except for * geometric mean (68% confidence intervals), # median, (range)
Juniper Asthma Control Score

- **FENO group**
- **Control Group**

Mean inhaled corticosteroid dose
Figure 3 Changes in Juniper Asthma Control Score, FE\textsubscript{NO} and mean daily dose of inhaled corticosteroid. Points are mean (SEM) except for *geometric mean (Log SE).
Time elapsed (months)

No. of Exacerbations

19 patients, 26 exacerbations
12 patients, 18 exacerbations

$p=0.43$
Figure 4 Cumulative exacerbations in the control and FeNO group.
Eos=3%

FENO group
Control group

Differential sputum eosinophil count

\( \text{Differential sputum eosinophil count} \times 100 \)
Figure 5 Scatter plot of baseline $F_{ENO}$ against baseline differential sputum eosinophil count. Corresponding cut off points for $F_{ENO} = 26$ ppb and eosinophils= 3% are drawn as lines.
Reference List


Ref Type: Report


Ref Type: Generic


treatment by monitoring sputum cell counts: effect on exacerbations.

