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# Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma

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## ABSTRACT

### BACKGROUND

International guidelines for the treatment of asthma recommend adjusting the dose of inhaled corticosteroids on the basis of symptoms, bronchodilator requirements, and the results of pulmonary-function tests. Measurements of the fraction of exhaled nitric oxide ($Fe_{NO}$) constitute a noninvasive marker that may be a useful alternative for the adjustment of inhaled-corticosteroid treatment.

### METHODS

In a single-blind, placebo-controlled trial, we randomly assigned 97 patients with asthma who had been regularly receiving treatment with inhaled corticosteroids to have their corticosteroid dose adjusted, in a stepwise fashion, on the basis of either $Fe_{NO}$ measurements or an algorithm based on conventional guidelines. After the optimal dose was determined (phase 1), patients were followed up for 12 months (phase 2). The primary outcome was the frequency of exacerbations of asthma; the secondary outcome was the mean daily dose of inhaled corticosteroid.

### RESULTS

Forty-six patients in the $Fe_{NO}$ group and 48 in the group whose asthma was treated according to conventional guidelines (the control group) completed the study. The final mean daily doses of fluticasone, the inhaled corticosteroid that was used, were 370 μg per day for the $Fe_{NO}$ group (95 percent confidence interval, 263 to 477) and 641 μg per day for the control group (95 percent confidence interval, 526 to 756; P=0.003), a difference of 270 μg per day (95 percent confidence interval, 112 to 430). The rates of exacerbation were 0.49 episode per patient per year in the $Fe_{NO}$ group (95 percent confidence interval, 0.20 to 0.78) and 0.90 in the control group (95 percent confidence interval, 0.31 to 1.49), representing a nonsignificant reduction of 45.6 percent (95 percent confidence interval for mean difference, −78.6 percent to 54.5 percent) in the $Fe_{NO}$ group. There were no significant differences in other markers of asthma control, use of oral prednisone, pulmonary function, or levels of airway inflammation (sputum eosinophils).

### CONCLUSIONS

With the use of $Fe_{NO}$ measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control.

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Inhaled corticosteroids are the mainstay of treatment for chronic asthma, the doses of which should be adequate to control asthma symptoms but also as low as possible in order to prevent adverse effects. Since the dose required is highly variable, both among patients and within individual patients, physicians need an easy, effective, and safe method to guide dose titration. Current treatment guidelines recommend that adjustments in doses should be based on asthma symptoms and the results of basic pulmonary-function tests. Two proof-of-concept studies have demonstrated that the use of alternative criteria — namely, airway hyperresponsiveness[1] or eosinophilia in induced sputum[2] — to make adjustments in doses of inhaled corticosteroids leads to improved outcomes. However, these particular measurements may be time-consuming to obtain or difficult to perform.

The fraction of nitric oxide in the exhaled air ($Fe_{NO}$) is a marker of asthma; the magnitude of $Fe_{NO}$ is increased in proportion to bronchial wall inflammation[3] or induced-sputum eosinophilia[4] as well as to airway hyperresponsiveness.[4,5] Increases in $Fe_{NO}$ are associated with a deterioration in asthma control,[5] and $Fe_{NO}$ levels are reduced in a dose-dependent manner with antiinflammatory treatment.[6,7] However, unlike induced-sputum analysis and bronchial-challenge testing, $Fe_{NO}$ measurements are easy to perform, reproducible, and associated with a high degree of acceptance by patients.[8]

Taken together, these data suggest that $Fe_{NO}$ measurements may provide a method of adjusting inhaled corticosteroid doses for patients with chronic asthma. In a prospective, randomized, single-blind, placebo-controlled trial, we compared the adjustment of the dose of an inhaled corticosteroid, fluticasone, with use of a $Fe_{NO}$-based algorithm with adjustment with use of an algorithm based on guidelines promulgated by the Global Initiative for Asthma.[9] This study was designed to test the null hypothesis that there would be no difference in the frequency of asthma exacerbations between the two approaches.

## METHODS

### PATIENTS

We recruited 110 patients 12 to 75 years of age with chronic asthma[10] whose treatment was being managed in a primary care setting. Each patient had received regular inhaled corticosteroids for six months or more, with no change in dose within the previous six weeks. Exclusion criteria included the following: four or more courses of oral prednisone in the previous 12 months; admission to the hospital because of asthma in the previous 6 months or to the intensive care unit because of asthma at any time in the past; and cigarette smoking, either current or past, with a history of more than 10 pack-years. The use of long-acting beta-agonists was discontinued because of the recognized confounding effect of these agents on asthma exacerbations — the primary end point of the study. However, subjects who were unable to tolerate the attempted withdrawal of long-acting beta-agonists during the run-in period were allowed to participate in the study if they could continue the use of these agents at a fixed dose.

### STUDY PLAN

The study plan is outlined in Figure 1. Exhaled nitric oxide was measured and spirometry performed after a two-week run-in period and at every visit thereafter. At the second visit, all patients were started on inhaled fluticasone (Flixotide, GlaxoSmithKline), administered twice daily with the use of a combination of two identical, unmarked metered-dose inhalers (in order to achieve complete blinding at all times). The fluticasone was given through a large volume spacer (Volumatic, GlaxoSmithKline). Six treatment doses were available: 1000 μg, 750 μg, 500 μg, 250 μg, and 100 μg per day, and placebo (0 μg). At each visit, treatment packs were dispensed that contained two inhalers; these provided the requisite combination of 0 μg, 50 μg, 125 μg, and 250 μg per puff, which enabled the patient to receive the total daily dose as one puff from each inhaler twice daily at all times during the study. Subjects were informed that treatment could vary between 0 and 1000 μg per day, but they were not informed of the actual prescribed dose at any time.

#### *Phase 1*

During phase 1, the dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 μg per day to start (or 500 μg per day if their inhaled-corticosteroid requirement before enrollment was less than 200 μg per day of fluticasone or the equivalent). Subjects returned after four weeks and were randomly assigned to one of the two management groups (the group receiving conventional management, hereafter referred to as the control group, and the group in which $Fe_{NO}$

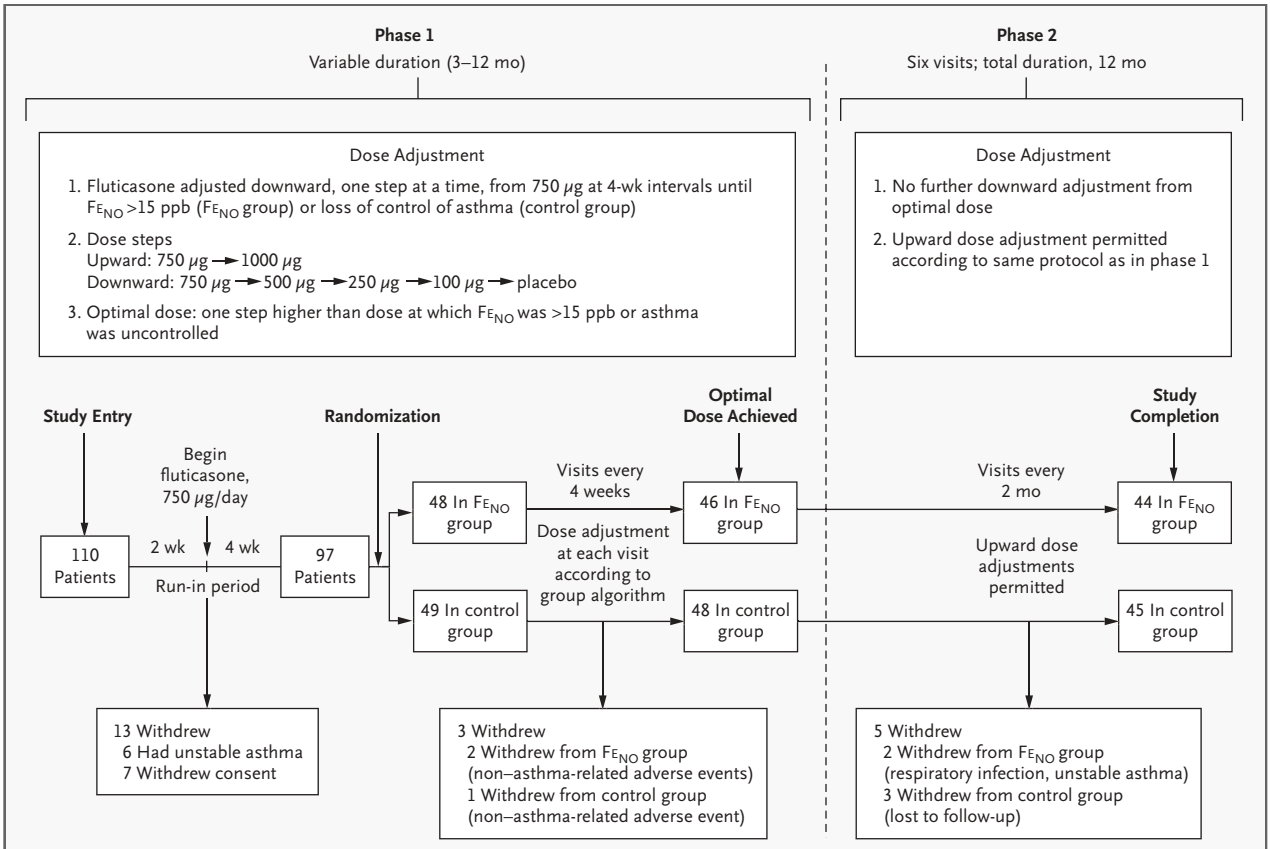


**Figure 1. The Study Plan.**

At the end of the run-in period, patients began receiving 750 μg of fluticasone per day. The dose was then adjusted at each visit according to each patient's assigned algorithm. Patients who were taking less than 200 μg of fluticasone per day (or the equivalent dose of budesonide or beclomethasone) at study entry began receiving 500 μg per day. The dose could be increased, to a maximum of 1000 μg per day, if the measured $FE_{NO}$ was greater than 15 parts per billion (ppb) or if asthma remained uncontrolled. The criteria by which loss of control of asthma was determined are listed in Table 1. If, during phase 2, after an upward adjustment, asthma was subsequently found to be controlled at two consecutive visits (i.e., for four months), the dose of fluticasone was reduced by one step — but not below the optimal dose or to 0 μg per day.

was used as the basis for dose adjustment), with each group having a different algorithm for titration of the dose of fluticasone (Table 1). Subjects were blinded to their group assignment.

The control-group algorithm was derived from criteria established by the Global Initiative for Asthma 2002 for the control of asthma.[9] Dose adjustments were based on predetermined thresholds in regard to symptoms, bronchodilator use, diurnal peak flows, and spirometry. The $FE_{NO}$-group algorithm was based solely on $FE_{NO}$ measurements, with 15 parts per billion (ppb) of nitric oxide (at an exhaled flow rate of 250 ml per second) used as the cutoff point, above which an increase in the dose of inhaled corticosteroid was prescribed[5]; this $FE_{NO}$ value is equivalent to 35 ppb at a flow rate of 50 ml per second (see part 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). At each study visit, with the use of the appropriate algorithm, the patient's asthma was deemed to be controlled or uncontrolled. The dose of inhaled fluticasone was decreased or increased (to a maximum of 1000 μg per day) accordingly.

Titration downward was repeated one step at a time every four weeks until the $FE_{NO}$ was greater than 15 ppb or until asthma became uncontrolled (Table 1), at which point the dose of fluticasone was increased — again, one step at a time, at four-week intervals, until the $FE_{NO}$ level was less than 15 ppb or until asthma was again controlled. Once the $FE_{NO}$ level had decreased to less than 15 ppb, or asthma control had been reestablished, the final

**Table 1. Criteria for Adjustment of the Dose of Inhaled Corticosteroid in the Two Study Groups.***

| Group | Asthma Controlled?† | |
|---|---|---|
| | Yes | No |
| **Control‡** | | |
| Asthma symptoms§ | Present ≤2 days/wk (24-hr scores of 1 of 5 not counted) | Present >2 days/wk with 24-hr asthma score ≥2 of 5 |
| Nighttime waking (nights/wk) | ≤1 | >1 |
| Bronchodilator use | ≤4 Occasions/wk and on ≤2 days/wk | >4 Occasions/wk or on >2 days/wk |
| Variation in PEFR (amplitude % of mean, previous 7 days)‡ | ≤20 | >20 |
| $FEV_1$ (% of baseline) | ≥90 | <90 |
| **Exhaled nitric oxide** | | |
| $F_{ENO}$ (ppb at 250 ml/second) | <15 | ≥15 |

* PEFR denotes peak expiratory flow rate, $FEV_1$ forced expiratory volume in one second, and ppb parts per billion.
† For asthma to be considered controlled, a yes answer was required in each of the five categories for the control group; for asthma to be considered uncontrolled, a no answer was required in at least one category.
‡ Data were obtained from patient diaries for seven days before the study visit.
§ Asthma symptoms were given a score of 0 to 5, with 5 being the most severe.

dose (which possibly included placebo among patients in whom asthma control was not lost at a dose of 0 μg of fluticasone per day) was deemed to be the optimal dose for that person.

*Phase 2*

During phase 2, which lasted for 12 months, maintenance treatment with inhaled fluticasone was continued at the optimal dose, although further upward adjustments in the dose were permitted if asthma control was lost. Subjects were evaluated on six occasions at intervals of two months. At each visit, $F_{ENO}$ measurements were obtained or asthma control was assessed in the same way as during phase 1. If the $F_{ENO}$ was greater than 15 ppb or asthma was uncontrolled at any visit during phase 2, treatment was increased by one step in accordance with the assigned algorithm. Thereafter, if the $F_{ENO}$ level remained at less than 15 ppb or if the asthma was controlled for two consecutive visits (i.e., for four months), the dose was titrated back down one step. However, treatment was not decreased below the optimal dose (below which each patient had previously demonstrated instability) or to placebo during phase 2.

All treatment orders were verified independently by an investigator who was blinded to the treatment assignments. (See part 2 of the Supplementary Appendix for full details regarding the treatment-assignment protocol.) Compliance was determined according to the weight of the study inhalers.

### BACK-UP STRATEGY FOR THE $F_{ENO}$ GROUP

We did not have a priori evidence that low $F_{ENO}$ measurements could reliably be used to deny patients an increase in inhaled-corticosteroid dose that by all other criteria would be deemed clinically necessary. Thus, for ethical reasons, subjects in the $F_{ENO}$ group had a predetermined "safety buffer" by which an upward (one-step) adjustment in the dose was provided to deal with deteriorating asthma in the absence of a rise in measured $F_{ENO}$. The criteria for intervention can be found in part 3 of the Supplementary Appendix.

Patients were not permitted to adjust their maintenance dose of inhaled corticosteroid except at a study visit. However, again for reasons of safety, all subjects had a personalized self-management plan, which instructed them to take oral prednisone, 40 mg per day, when morning peak flows fell below 70 percent of mean run-in values; they continued this dose until peak flows increased above 85 percent, at which time they were to take 20 mg per day for the same number of days. Participants had 24-hour access to the study investigators.

### MEASUREMENTS

Exhaled nitric oxide was measured in accordance with the recommendations of the American Thoracic Society[11] at a flow rate of 250 ml per second. Additional information regarding technical aspects of $F_{ENO}$ measurements is contained in part 1 of the Supplementary Appendix. Spirometry was performed according to the American Thoracic Society criteria.[12] Sputum induction was performed on three occasions: at the first, "uncontrolled," visit during phase 1; at the final visit of phase 1, which occurred after four weeks of treatment with the optimal dose of fluticasone; and at the final visit of phase 2. Sputum was obtained and analyzed according to published methods with a whole-sample technique.[13,14]

Subjects completed a daily diary card throughout the study period to record symptoms, the use of bronchodilators, peak flows, and the use of prednisone. Asthma symptoms were scored for each 24-hour 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,

**Table 2. Criteria for Daily Asthma Score Used for the Calculation of Exacerbations.***

| Daily Asthma Score | Scoring Criteria |
|---|---|
| 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:<br>Bronchodilator use on 2 or more occasions in 24 hr more than rounded mean number of occasions during the run-in period<br>Increase in symptom score of 1 point or more as compared with rounded mean during run-in period<br>Onset of or increase in nocturnal waking: 1 or more times in previous 7 nights more than rounded mean no. of times during the run-in period<br>or<br>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 run-in period and one or more criteria for an asthma score of 1<br>or<br>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<br>or<br>Attendance at clinician's office or emergency department because of severe asthma |

* Modified from Taylor et al.[15] PEFR denotes peak expiratory flow rate.
† The best PEFR did not include any recording made within six hours after the use of a bronchodilator.

4 symptoms most of the time that did affect normal daily activities, and 5 symptoms so severe as to disrupt daily activities.

From the data provided in the diary, a global asthma score of 0 to 4 was calculated for each 24-hour period with the use of previously published criteria (Table 2).[15] The frequencies of days with scores of 0, 1, 2, 3, and 4 were used to describe the control of asthma during phase 2. The same scoring system was used to calculate the frequency, duration, and severity of exacerbations of asthma during phase 2. The criteria for distinguishing between minor and major exacerbations and their duration have been published previously.[15] Briefly, a minor exacerbation was defined as a global daily asthma score of 2 on two or more consecutive days; a major exacerbation as a global daily asthma score of 3 on two or more consecutive days (or in one day, in the context of a minor exacerbation); a major exacerbation or medical emergency as a global daily asthma score of 4 in one day; and the conclusion of an exacerbation as a global daily asthma score that had returned to and remained at 0 or 1 for three or more days — otherwise the exacerbation was deemed to be continuing. The number of courses of prednisone for the treatment of asthma exacerbations was designated as a secondary end point; this end point was independent of the criteria used to calculate rates of exacerbation.

### STUDY SIZE AND STATISTICAL ANALYSIS

In the studies by Sont et al.[1] and Green et al.,[2] the use of algorithms based on measurements of airway responsiveness and sputum cell counts resulted in a reduction in exacerbations of 47 percent and 68 percent, respectively. Using data on exacerbation rates obtained from a previous study carried out in our population,[15] we calculated with the use of the $FE_{NO}$ algorithm that 42 patients per group who completed the study would be required to demonstrate a 60 percent reduction in the rate of exacerbations. The data for patients who withdrew during phase 2 were analyzed on an intention-to-treat basis, and annual exacerbation rates were calculated by extrapolation. The analysis of the rates of total, minor, and major asthma exacerbations was performed with the use of negative binomial regression.

The analysis of the mean daily dose of fluticasone was performed with the use of analysis of covariance, with the fluticasone-equivalent dose at study entry as the covariate. The distribution of doses of inhaled corticosteroids was compared with the use of the Kolmogorov–Smirnov Z test. Sputum cell counts and $FE_{NO}$ data were analyzed after logarithmic transformation. Other normally distributed data were analyzed with use of the two-sample t-test. Results are expressed as means with 95 percent confidence intervals unless stated otherwise.

### ETHICS

The study was approved by the Otago ethics committee, and all participants gave written informed consent. The authors were solely responsible for the study design, data analysis, and interpretation and for the writing of the manuscript.

## RESULTS

One hundred ten patients were recruited, 69 of them (63 percent) women, with a mean age of 44.8 years (range, 12 to 73) and a mean duration of asthma of 25.2 years (range, 1 to 65). Seven patients withdrew consent before randomization, and six had unstable asthma. Ninety-seven patients underwent randomization to a management group. Baseline measurements are shown in Table 3. The mean dose of inhaled corticosteroid at study entry was not significantly different in the two management groups — 411 μg per day of fluticasone or the equivalent (95 percent confidence interval, 344 to 478) in the $FE_{NO}$ group and 491 μg per day (95 percent confidence interval, 403 to 579) in the control group. Among the 19 patients who were taking long-acting beta-agonists at study entry, the use of these agents was continued in 5 of 9 patients in the $FE_{NO}$ group and in 8 of 10 in the control group.

Three patients withdrew during phase 1 (two in the $FE_{NO}$ group, because of a breast lump and gout, respectively, and one in the control group because of a respiratory tract infection). Thus, 94 patients (46 in the $FE_{NO}$ group and 48 in the control group) completed phase 1 and entered phase 2. Five patients withdrew during phase 2 but were included in the intention-to-treat analysis (two in the $FE_{NO}$ group, because of a respiratory tract infection in one and unstable asthma despite taking the maximum dose of fluticasone in the other, and three from the control group, all of whom were lost to follow-up). There were no significant differences in the duration of phase 1 for the two groups — mean, 25.4 weeks for the $FE_{NO}$ group (95 percent confidence interval, 23.2 to 27.7) and 22.4 weeks for the control group (95 percent confidence interval, 20.2 to 24.7; P=0.07).

### ASTHMA CONTROL, EXACERBATIONS, AND USE OF PREDNISONE

The total rate of exacerbations during phase 2 was 0.49 exacerbation per patient per year in the $FE_{NO}$ group (95 percent confidence interval, 0.20 to 0.78) and 0.90 in the control group (95 percent confidence interval, 0.31 to 1.49; P=0.27). This 45.6 percent reduction among patients in the $FE_{NO}$ group (95 percent confidence interval, −78.6 to 54.5) failed to confirm the superiority of the $FE_{NO}$ algorithm (for which a threshold of 60 percent reduction had been deemed clinically significant). There were no statistically significant differences between the two groups in the exacerbation rates (Fig. 2A), the cumulative total numbers of exacerbations (Fig. 2B), the times to a first exacerbation (Fig. 2C), or the numbers of patients with one or more exacerbations (Fig. 2D). The number of patients who had at least one exacerbation was numerically, but not significantly, greater in the $FE_{NO}$ group (14 of 46, as compared with 11 of 48 in the control group; P=0.39) (Fig. 2C), whereas the overall frequency of exacerbations per patient was higher in the control group (P=0.27) (Fig. 2B and 2D). This pattern could not be accounted for by the frequency of safety interventions that occurred in the $FE_{NO}$ group.

During phase 2, there were no significant differences in nighttime waking or use of bronchodilators among patients in the $FE_{NO}$ and control groups (Table 3). The percentage of symptom-free days was similar in the two groups (69.3 percent in the $FE_{NO}$ group and 63.7 percent in the control group, P=0.44), and the number of courses of prednisone that were used did not differ significantly — 22 in the $FE_{NO}$ group and 29 in the control group (P=0.60). The percentages of patients who required treatment with prednisone during phase 2 were as follows: zero courses of treatment, 71.7 percent in the $FE_{NO}$ group and 68.8 percent in the control group; one course, 17.4 percent and 18.8 percent, respectively; and two or more courses, 10.9 percent and 12.5 percent, respectively.

### DOSES OF INHALED CORTICOSTEROID

At the end of phase 1, the mean fluticasone dose was 292 μg per day in the $FE_{NO}$ group (95 percent

**Table 3. Demographic and End-Point Data for All Randomized Patients.***

| Variable | Baseline | | First Uncontrolled Visit | | Optimal Dose | | Final Visit | |
|---|---|---|---|---|---|---|---|---|
| | $Fe_{NO}$ (N=48) | Control (N=49) | $Fe_{NO}$ (N=30) | Control (N=38) | $Fe_{NO}$ (N=46) | Control (N=48) | $Fe_{NO}$ (N=46) | Control (N=48) |
| | *mean (95 percent confidence interval)* | | | | | | | |
| Diary data | | | | | | | | |
| Symptom score (daily score, previous 7 days) | 0.6 (0.4–0.8) | 0.8 (0.6–1.1) | 1.2 (0.8–1.6) | 1.4 (1.2–1.7) | 0.5 (0.3–0.8) | 0.5 (0.3–0.8) | 0.4 (0.1–0.7) | 0.6 (0.4–0.9) |
| P value | | | P=0.36 | | P=0.99 | | P=0.23 | |
| Nocturnal waking (nights/week, previous 7 days) | 0.4 (0.1–0.7) | 0.3 (0.0–0.5) | 1.1 (0.4–1.8) | 1.0 (0.5–1.5) | 0.3 (0.0–0.6) | 0.3 (0.0–0.5) | 0.2 (0.0–0.6) | 0.2 (0.0–0.4) |
| P value | | | P=0.73 | | P=0.96 | | P=0.89 | |
| Bronchodilator use (occasions/day, previous 7 days) | 0.5 (0.2–0.8) | 0.6 (0.3–0.8) | 1.8 (0.6–2.9) | 2.8 (1.3–4.3) | 0.5 (0.2–0.8) | 0.4 (0.2–0.6) | 0.4 (0.1–0.7) | 0.4 (0.1–0.6) |
| P value | | | P=0.32 | | P=0.56 | | P=0.98 | |
| Asthma score (% of days) | | | | | | | | |
| 0 | — | — | — | — | 83.2 (78.1–88.3) | 81.3 (76.7–85.9) | 85.2 (78.4–92.0) | 78.5 (70.4–86.6) |
| 1 | — | — | — | — | 15.8 (10.9–20.7) | 17.2 (12.8–21.6) | 14.0 (7.4–20.6) | 19.9 (12.3–27.5) |
| ≥2 | — | — | — | — | 1.0 (0.5–1.5) | 1.5 (0.6–2.4) | 0.8 (0.3–1.3) | 1.7 (0.3–3.1) |
| P value | | | | | P=0.52 | | P=0.19 | |
| Lung function | | | | | | | | |
| $FEV_1$ (% of predicted value) | 86.4 (80.6–92.2) | 83.1 (76.5–89.7) | 76.0 (67.4–84.6) | 77.7 (69.8–85.6) | 85.2 (79.4–91.0) | 83.8 (77.5–90.1) | 86.1 (80.6–91.6) | 82.3 (75.8–88.8) |
| P value | | | P=0.78 | | P=0.74 | | P=0.39 | |
| Morning peak flow (mean, previous 7 days) | 394 (363–424) | 395 (365–424) | 375 (339–411) | 391 (355–428) | 393 (364–422) | 400 (370–431) | 404 (373–436) | 403 (371–435) |
| P value | | | P=0.54 | | P=0.73 | | P=0.94 | |
| Other measurements | | | | | | | | |
| Exhaled NO (geometric mean ppb) | 7.8 (6.6–9.3) | 6.4 (5.5–7.5) | 18.2 (15.9–20.8) | 8.4 (6.5–10.9) | 8.2 (7.0–9.5) | 6.5 (5.2–8.1) | 8.6 (7.5–9.9) | 7.6 (6.4–9.1) |
| P value | | | P<0.001 | | P=0.10 | | P=0.29 | |
| Sputum eosinophils (geometric mean %) | — | — | 8.0 (4.7–13.8) | 2.1 (1.1–4.1) | 2.5 (1.7–3.7) | 1.7 (1.0–2.8) | 1.1 (0.7–1.8) | 1.2 (0.7–2.0) |
| P value | | | P=0.004 | | P=0.22 | | P=0.88 | |

* Data were obtained at study entry; at the first visit; when exhaled nitric oxide (NO) was increased to more than 15 parts per billion (ppb) in the patients in the $Fe_{NO}$ group or asthma was uncontrolled in the control group; at the end of phase 1, when the optimal dose was determined; and at the end of phase 2. CI denotes confidence interval, and $FEV_1$ forced expiratory volume in one second. P values refer to comparisons between the $Fe_{NO}$ group and the control group.

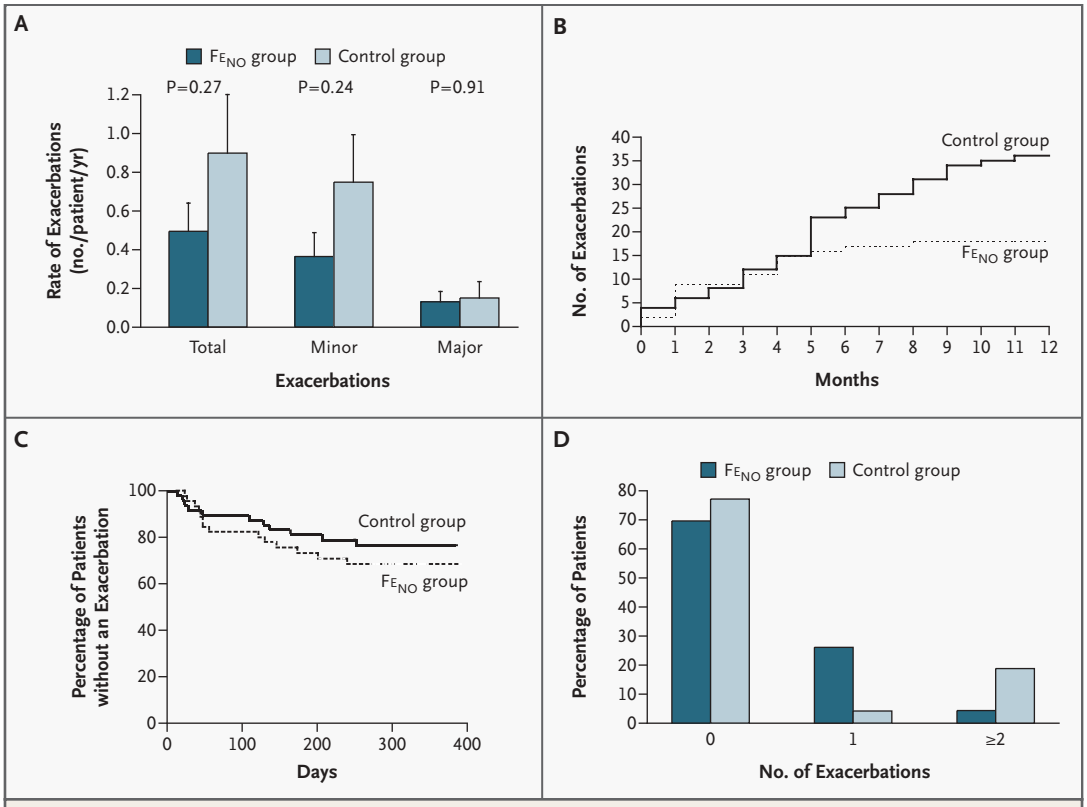


**Figure 2. Rates of Exacerbation.**

Panel A shows the mean rates of total exacerbations of asthma and of minor and major exacerbations during phase 2. Error bars represent SEs. In Panel B, the cumulative number of exacerbations of asthma during phase 2 is shown; P=0.27 for the comparison between groups. Panel C shows the results of a Kaplan–Meier analysis of the time to a first exacerbation of asthma in each group during phase 2. There was no significant difference between the two groups (P=0.39). Panel D shows the frequency distribution of patients who had zero, one, and two or more exacerbations during phase 2.

confidence interval, 188 to 396) and 567 μg per day in the control group (95 percent confidence interval, 443 to 691; P=0.003); the median doses were 100 μg per day (25th and 75th percentiles, 0 and 500) and 750 μg per day (25th and 75th percentiles, 100 and 1000), respectively. The mean fluticasone doses at the end of phase 2 were 370 μg per day in the $FE_{NO}$ group (95 percent confidence interval, 263 to 477) and 641 μg per day in the control group (95 percent confidence interval, 526 to 756; P=0.003); the median doses were 100 μg per day (25th and 75th percentiles, 100 and 750) and 750 μg per day (25th and 75th percentiles, 100 and 1000), respectively (Fig. 3A).

The mean difference in dose between groups was 270 μg per day (95 percent confidence interval, 112 to 430). The distribution of fluticasone doses at the final study visit differed significantly between groups (P=0.008) (Fig. 3B). In the $FE_{NO}$ group, safety-buffer criteria were used for dose adjustment on 16 occasions (out of 436 assessments), for reasons of clinically significant symptoms (in 10 patients), reduced pulmonary function (4 patients), or both (2 patients) in the absence of a rise in $FE_{NO}$ to greater than 15 ppb. The percentage of patients who complied with medication use was 84.8 percent in the $FE_{NO}$ group and 89.8 percent in the control group, with compliance defined as consumption of 75 percent or more of the study medication as determined by weight.

### SPUTUM CELL COUNTS, $FE_{NO}$ MEASUREMENTS, AND PULMONARY FUNCTION

Changes in the indexes of airway inflammation and pulmonary function are reported in Table 3. The magnitude of airway inflammation, as measured by

the percentage of eosinophils in induced sputum and $FE_{NO}$ measurements, was not significantly different between the two study groups at the end of either phase 1 or phase 2. At the end of phase 2, 65.8 percent of patients in the $FE_{NO}$ group and 65.9 percent in the control group had sputum eosinophil counts of less than 3 percent. Only at the time of the visit at which airway inflammation or asthma was deemed to be uncontrolled (i.e., the first, uncontrolled, visit) were significant increases in $FE_{NO}$ and sputum eosinophils noted in the $FE_{NO}$ group. This finding confirms the appropriateness of the step up in dose that was undertaken on that occasion.

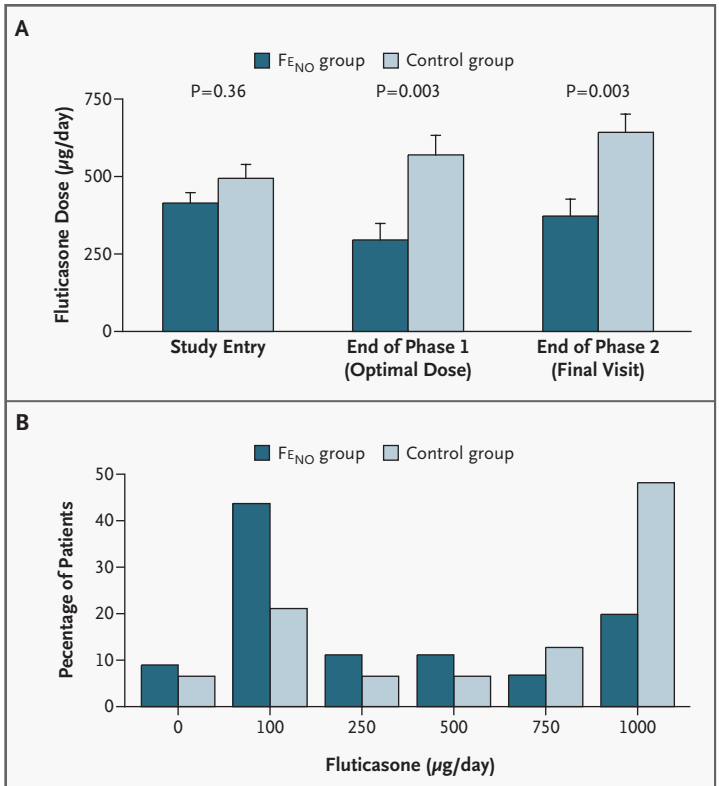


**Figure 3. Doses of Inhaled Fluticasone.**

Panel A shows the mean dose of inhaled fluticasone at study entry, the optimal dose, and the dose at the final visit. Error bars represent SDs. Panel B shows the distribution of doses of inhaled fluticasone at the end of the study. P=0.008 for the comparison between the two groups.

## DISCUSSION

In our study, the use of $FE_{NO}$ measurements that were performed on a regular basis in patients with asthma resulted in a lower maintenance dose of inhaled corticosteroid needed to control the asthma, as compared with the use of a dose-adjustment strategy based on conventional guidelines. We demonstrated a 40 percent reduction in the required dose of inhaled corticosteroid without compromising any major clinical outcomes, including exacerbation rates and prednisone use. Despite the significantly lower optimal dose of inhaled corticosteroid in the $FE_{NO}$ group, the sputum eosinophil counts were no different: in both management groups, the mean cell counts at the end of both phases were within previously defined limits of acceptability (<3 percent).[16] The mean dose requirement in the $FE_{NO}$ group was 370 μg per day, which is consistent with the results of a recent meta-analysis indicating that the major benefits of fluticasone are usually achieved at 500 μg or less per day.[17] Among the patients whose asthma treatment was adjusted with the use of the algorithm based on conventional guidelines, the mean dose was 641 μg per day, suggesting that excessive doses were being used.

The outcomes obtained with the use of $FE_{NO}$ measurements are inevitably dependent on the cutoff point used to signal the likelihood of active airway inflammation (defined in this study as 15 ppb at a flow rate of 250 ml per second, the equivalent of 35 ppb at 50 ml per second). It could be argued that asthma control remained suboptimal even with a mean rate of exacerbations of 0.49 event per patient per year in the $FE_{NO}$ group. If a lower cutoff point — for example, 10 ppb — had been used, higher mean doses of inhaled corticosteroid would have been required in the $FE_{NO}$ group, which in turn might have resulted in a further reduction in the exacerbation rate such that the superiority of the use of $FE_{NO}$ measurements as a dose-adjustment strategy would have been confirmed. The chosen cutoff point for our study was based on previous work that showed that a $FE_{NO}$ level of 15 ppb (at a flow rate of 250 ml per second) yielded the best overall positive and negative values on the basis of which to predict an upcoming loss of asthma control.[5] This number is also consistent with the recently published data that outline the "normal range" of $FE_{NO}$ levels.[8] Our choice of 15 ppb for the cutoff point may also explain the subtle differences in outcome between the present study and that of Green et al.[2]

There is some debate about the optimal strategy for dose adjustment of inhaled corticosteroids in clinical practice. Both "step-up" and "step-down" approaches are advocated. However, there is agreement among international guidelines that after the

control of asthma has been established, titration downward to the minimal necessary doses of inhaled corticosteroids ought to be undertaken.[9,18] This has been tested in randomized controlled trials.[19-21] In one study in which downward titration was used, patients required 25 percent less inhaled corticosteroid during the one-year follow-up than did patients in the control group, yet without any loss of asthma control.[19] In our study, however, downward titration with the use of the predominantly symptom-based algorithm to define poor asthma control was possible in only a minority of patients. In contrast, when $FE_{NO}$ measurements were used, we could readily identify patients in whom a reduction in the dose of inhaled corticosteroid could be appropriately achieved. Regardless of the approach taken, the clinician is faced with significant heterogeneity in the dose–response to inhaled corticosteroid for individual patients,[22] and this may not be determined easily on the basis of either symptoms or pulmonary function.

An alternative explanation for our results is that in the control group, the dose of inhaled corticosteroid was much higher than necessary. This may have occurred because, just as in the case of the $FE_{NO}$ algorithm, dose adjustments of inhaled corticosteroids depend on the thresholds used to determine "uncontrolled" asthma, and these thresholds may have been inappropriate. In our study, only one of five criteria had to be met in order to determine poor asthma control. Furthermore, it can be argued that within each category the cutoff points that were used, particularly for symptoms and use of bronchodilators, were too low. Each of the chosen cutoff points was consistent with current international guidelines that advocate the minimization of symptoms and of bronchodilator use as a goal of asthma therapy. Although we agree with this principle, our results highlight the possibility that the rigorous application of these guidelines may in fact be problematic. All the more reason, then, for the monitoring of an objective measure of airway pathology to complement the assessment of patients with symptomatic asthma so that appropriate choices of treatment can be made.

In the recent Gaining Optimal Asthma Control Study,[23] the investigators sought to achieve asthma control among patients in two groups with "step-up" titration of either a combination of salmeterol and fluticasone or fluticasone alone with the use of a symptoms-based algorithm. Remarkably, "total control" was achieved among only 41 percent of the patients receiving salmeterol and fluticasone and among 28 percent of those receiving fluticasone alone, despite doses of 1000 μg of fluticasone per day administered to 68 percent and 76 percent of patients, respectively. The median dose requirement was 1000 μg per day in each treatment group, which is similar to the requirement for patients in the control group in our study, in which a similar dose-adjustment strategy was used (48 percent of patients required 1000 μg per day). Together, these outcomes strongly suggest that the use of clinical end points as the basis for adjustments in doses of inhaled corticosteroids has substantial limitations and may lead to higher doses than are appropriate for many patients. In our study, we did not allow for the concomitant use of long-acting beta-agonists; this would have required a much larger study. However, the results obtained in our control group strongly support a role for therapy with long-acting beta-agonists for patients who remain symptomatic despite optimal corticosteroid treatment. This is in keeping with a stepwise approach to asthma management.[18]

In conclusion, we have shown that in patients with chronic, persistent asthma, treatment with inhaled corticosteroids can successfully be titrated with the use of $FE_{NO}$ measurements. The use of $FE_{NO}$ measurements may also help to minimize the potential long-term side effects that are related to inhaled corticosteroids and are more likely when higher doses are used.[24] $FE_{NO}$ measurements are easy to perform, can be reproduced accurately, and provide immediate results on which the practitioner can act. Overall, this approach offers a logical alternative to the use of clinical data alone as the basis for dose adjustment of inhaled corticosteroids in the management of asthma.

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