

Can exhaled nitric oxide fraction predict adherence to inhaled corticosteroids in atopic and nonatopic children with asthma?



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Clinical Implications

- Fraction of exhaled nitric oxide appears to be a poor predictor of adherence in the overall population of children with asthma, being prescribed daily inhaled corticosteroid therapy. In children with poorly controlled atopic asthma, fraction of exhaled nitric oxide might be a useful marker of nonadherence.

TO THE EDITOR:

The fraction of nitric oxide in exhaled air (FENO) is a noninvasive marker of the degree of eosinophilic airway inflammation in children and adults with allergic asthma.^{1,2} FENO can be easily and reproducibly measured in children by chemoluminescence.² FENO decreases after institution of daily controller therapy with inhaled corticosteroids (ICSs), and increases when ICSs are withdrawn.^{1,3} This has led to the hypothesis that FENO measurements could be a useful proxy measure to assess adherence to daily ICS controller therapy. This hypothesis has not been tested in children with asthma.

This was an observational longitudinal cohort study of 2- to 12-year-old children with asthma, details of which have been published previously.^{4,5} All participating children had a pediatric pulmonologist's diagnosis of persistent asthma and were using low-to-moderate doses of fluticasone propionate delivered by age-appropriate inhaler devices, the correct use of which was trained and checked by dedicated pediatric asthma nurses. During the 1-year study period, daily controller therapy was adjusted on the basis of the degree of asthma control achieved, following the Dutch national guideline for asthma, which is comparable to international asthma management guidelines.

Adherence was assessed by Smartinhaler (for metered dose inhaler/spacer combinations) and SmartDisk devices, validated electronic adherence loggers that record the date and time of each actuation on a microchip.⁶ Adherence was calculated as the ratio between the Smartinhaler/SmartDisk-recorded dosages and the prescribed dosages, expressed as a percentage, censored at 100%.⁵ At follow-up visits after 6- or 12-month follow-up, FENO was measured according to European Respiratory Society guidelines using the NIOX analyzer (Aerocrine, Solna, Sweden).⁷ During these follow-up visits, asthma control was assessed by parent-completed Asthma Control Questionnaire (ACQ, lower scores indicating better asthma control),⁸ by the attending physician (visual analogue scale score ranging from 0 to 100, higher scores indicating better asthma control), and by lung function before and after inhaling salbutamol 400 µg.

We analyzed the relation between FENO and ICS adherence, and adjusted this for asthma control, age, concomitant use of

nasal corticosteroids, and parental smoking in multiple regression analyses because these factors may have an impact on FENO. Subgroup analyses were performed for atopic children (based on sensitization to common inhalant allergens) and for atopic children with uncontrolled asthma. Analyses were performed with SPSS version 20 (IBM Corporation, Armonk, NY). The study was approved by the hospital's ethical review board. All parents provided written informed consent.

For this analysis, we used data of 60 children with a mean age of 8 years (range, 5-12 years), who succeeded in performing at least 1 FENO measurement at 6- or 12-month follow-up. The median FENO level was 14.0 ppb (interquartile range [IQR], 10-20 ppb). Median adherence to ICS was 82% (IQR, 56%-90%). Most children had well-controlled asthma as assessed by parents (median ACQ score, 0.5; IQR, 0-1) and by the attending physicians (median visual analogue scale score, 89; IQR, 85-95). Univariate analysis showed a statistically significant association of FENO with ICS adherence ($r = -0.45$, $P < .001$; Figure 1), FEV₁ before salbutamol ($r = -0.41$; $P = .002$), and change in FEV₁ after salbutamol ($r = 0.28$; $P = .035$). Multiple linear regression analysis showed that only adherence to ICS was independently associated with FENO ($P = .004$). FENO value of more than 25 ppb as a test for nonadherence (<80% of prescribed doses) had a sensitivity of 41%, a specificity of 94%, and a positive likelihood ratio of 6.8.

Forty-four children were sensitized to at least 1 aeroallergen. In these children with atopic asthma, FENO value of more than 25 ppb as a test for nonadherence (<80% of prescribed doses) had a sensitivity of 43%, a specificity of 96%, and a positive likelihood ratio of 9. Fourteen children with atopic asthma had uncontrolled asthma, based on a more than 11% improvement in FEV₁ after salbutamol or an ACQ score of more than 1.5. In 9 of these children, this was associated with adherence of more than 80%, in 7 of whom the FENO value was more than 25 ppb. All 6 children with adherence of more than 80% had FENO values of less than 25 ppb (Fisher exact test; $P = .021$).

This study shows that adherence to ICS is the only independent predictor of FENO in children with asthma. Asthma control and lung function were not associated with FENO when corrected for adherence to ICS. These findings are in agreement with 2 previous studies on FENO and adherence in children with asthma.^{3,9} In those studies, however, adherence was assessed by parental report or by device dose counters, which have been shown to be unreliable measures of true ICS adherence.¹⁰ The present study is the first to assess the reliability of FENO in predicting poor ICS adherence using highly reliable electronic measurement of adherence. Another strength of the study is that it was performed in regular asthma care, without any specific study intervention to promote adherence. Under these circumstances, the predictive value of FENO to identify poor adherence (<80%) in all children with asthma is too poor to be recommended for use in clinical practice. This is largely due to the high number of false negatives: many children with poor adherence have low FENO levels. This may be caused by the absence of exposure to viral infections, allergens, or other proinflammatory triggers. The generalizability of this study is limited because of the high median adherence level and good asthma control that

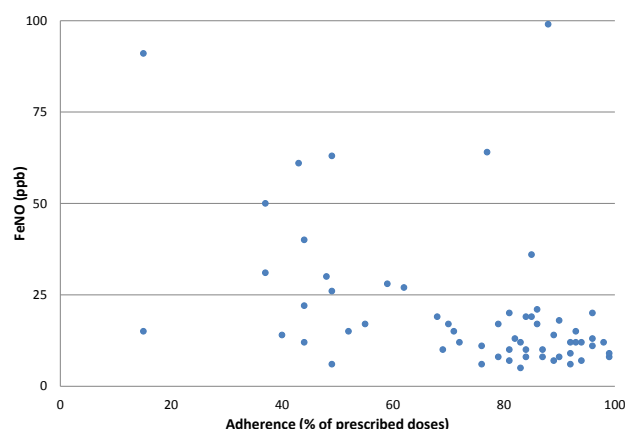


FIGURE 1. The relation between FeNO and electronically assessed adherence to ICSs.

we achieved, which is unusual in other asthma adherence studies. Because we also showed that poor adherence is commonly associated with low FeNO levels, we consider it unlikely that the random assessment of FeNO will perform better as a proxy measure of adherence in a cohort with lower median adherence levels and low FeNO levels.

Although the random assessment of FeNO appears to be a poor predictor of adherence in the overall population of children with asthma being prescribed daily ICS therapy, the results of the subgroup analysis of children with poorly controlled atopic asthma, characterized by eosinophilic inflammation, suggest that FeNO might be a useful marker of nonadherence in such patients. Further studies with larger sample sizes are required to confirm this, however, and our results do not support the use of FeNO as a marker of adherence in children with nonatopic or well-controlled asthma.

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