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Original Research

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Guideline-Recommended Fractional Exhaled Nitric Oxide Is a Poor Predictor of Health-care Use Among Inner-city Children and Adolescents Receiving Usual Asthma Care

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Background: **American Thoracic Society guidelines support using fractional exhaled nitric oxide (FENO) measurements in patients with asthma and highlight gaps in the evidence base. Little is known about the use of FENO levels to predict asthma exacerbations among high-risk, urban, minority populations receiving usual care.**

Methods: **Children with persistent asthma (n = 138) were enrolled in a prospective, observational cohort study and skin tested at baseline (a wheal ≥ 3 mm indicated a positive skin-prick test). FENO levels, lung function, and asthma-related health-care use were assessed at baseline and every 3 months thereafter for 1 year. Relationships between FENO levels and health-care use in the subsequent 3 months were examined. Final models accounted for repeated outcome measures and were adjusted for age, sex, and lung function.**

Results: **The mean age of the children was 11 years (range, 5-17 years), and most were male (57%), black (91%), and atopic (90%). At baseline, the median FENO level was 31.5 parts per billion (interquartile range, 16-61 ppb) and mean FEV_1/FVC was 80.7% (SD, ± 9.6%). There were 237 acute asthma-related health-care visits, 105 unscheduled doctor visits, 125 ED visits, and seven hospitalizations during the follow-up period. FENO level was not a significant predictor of acute visits, ED visits, unscheduled doctor visits, or hospitalization in either unadjusted or adjusted analyses. Use of recommended cut points did not improve the predictive value of the FENO level (positive predictive value, 0.6%-32.8%) nor did application of the guideline-based algorithm to assess change over time.**

Conclusions: **FENO level may not be a clinically useful predictor of health-care use for asthma exacerbations in urban minority children with asthma.** ***CHEST 2013; 144(3):923–929***

Abbreviations: ATS = American Thoracic Society; FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; NAEPP = National Asthma Education and Prevention Program; ppb = parts per billion

Although major strides in asthma management in the last 20 to 30 years have resulted in an overall reduction in asthma morbidity, there has been little impact on asthma morbidity among minority populations. New approaches to asthma management are needed to reduce morbidity for this high-risk population in particular. One approach is to identify biomarkers that predict exacerbations so that treatment can be intensified and risk of exacerbation mitigated. Measurement of fractional exhaled nitric oxide (FENO) has emerged as a candidate biomarker for just this application, since it is a noninvasive measure of pulmonary inflammation. Predicting exacerbations in high-risk groups such as urban minorities would be especially helpful as it would afford the opportunity to intervene before impending exacerbations, with the ultimate goal of reducing asthma morbidity.

A randomized controlled trial tested the efficacy of incorporating FENO measurements into asthma treatment decisions.[1] In this study, inner-city adolescents and young adults with moderate to severe asthma were randomized to one of two asthma management groups: the National Asthma Education and Prevention Program (NAEPP) guidelines-based asthma management group or the NAEPP guidelines plus FENO-based asthma management group. The study found that

implementation of guidelines-based care resulted in marked improvement in asthma outcomes and the addition of FENO measurement to guidelines-based care resulted in no additional benefit. An important question that remains, though, is whether FENO level, in a population receiving usual care, predicts future exacerbations, thereby identifying an opportunity to intervene to prevent exacerbations.

The American Thoracic Society (ATS) published clinical practice guidelines for interpretation of FENO levels, in which the strength of each recommendation and quality of supporting evidence are graded.[2] The guidelines make a strong recommendation for use of FENO level in monitoring airway inflammation in patients with asthma with low-quality supporting evidence. The guidelines also suggest strategies for interpreting FENO values, including use of cut points to interpret FENO values and an algorithm for interpreting significant increases in FENO level. However, the guidelines graded the strength of these recommendations as weak with low-quality supporting evidence, so additional data are needed to inform these recommendations. Therefore, we evaluated the performance of ATS clinical guideline-driven interpretation of FENO levels in predicting asthma-related health-care use in a predominantly urban, minority population receiving usual care.

Materials and Methods

Study Population

Data were drawn from the Mouse Asthma and Allergy Cohort Study, an institutional review board-approved (Johns Hopkins Institutional Review Board approval number NA_00006894), 1-year, observational, cohort study of 150 Baltimore City children. Participants were between ages of 5 and 17 years, inclusive, at enrollment; met NAEPP criteria for persistent asthma; had an exacerbation in the previous 12 months; and were nonsmokers. Written consent was obtained from parents/guardians of participants and assent obtained from participants. Study visits occurred at baseline, 3, 6, 9, and 12 months, and participants with at least two consecutive visits with valid FENO data were included in the analysis.

Study Visit Procedures

Skin-prick testing was performed to 14 allergens at the baseline visit using the MultiTest II device (Lincoln Diagnostics Inc) with positive histamine control and negative glycerol controls. Allergens tested were as follows: mouse; rat; cat; dog; *Dermatophagoides pteronyssinus*; *Dermatophagoides farinae*; American cockroach; German cockroach; oak; orchard grass; *Alternaria*, *Aspergillus*, and *Cladosporium* species; and ragweed. A positive skin test was defined as a net orthogonal wheal ≥ 3 mm. Atopy was defined as one or more positive skin tests.

Spirometry was performed at all study visits according to ATS guidelines using a KoKo spirometer (nSpire Health Inc) and National Health and Nutrition Examination Survey reference equations for calculating % predicted values.[3,4] A positive bronchodilator response was considered a 12% increase in FEV_1. FENO level was measured at all study visits using the Niox MINO (Aerocrine Inc) according to the ATS guidelines.[5,6]

The baseline questionnaire was administered by study staff and captured demographic information and pulmonary and allergic history. Health-care use for asthma during the previous 3 months was captured by questionnaire at all study visits. Symptoms during the previous 2 weeks were captured using standardized questions used in many inner-city asthma studies.[7] A "maximum symptom days" variable was constructed by taking the maximum of the following symptom variables: days of slowed activity; days of wheezing, coughing, or chest tightness when running or going upstairs; and nights of waking with asthma symptoms in the previous 2 weeks.[7]

Statistical Analysis

The primary outcome variable was asthma-related health-care use in the 3 months following the study visit during which FENO level and other clinical data were collected. Relationships between FENO concentrations and future health-care use were explored by displaying the distribution of FENO levels by health-care use and by cross tabulations of health-care use vs cut points of FENO level. A lag term was created to assess the relationship between FENO levels and events that occurred within the subsequent 3 months. Logistic regression with generalized estimating equations was used to account for repeated outcome measures and potential confounders. Analyses were performed with StataSE version 12.1 (StataCorp LP). A two-tailed P value $< .05$ was considered statistically significant.

Results

Study Population

The study population was predominantly black and of low socioeconomic status (Table 1). Ninety percent had at least one positive skin test, with 64% sensitized to cat, 59% to cockroach, 60% to rat, 56% to dust mite, and 51% to mouse. While children in the study were nonsmokers, they had exposure to secondhand smoke in the home environment, with 55% reporting secondhand smoke in the home and 87% having detectable

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Table 1—*Participant Characteristics*

Characteristic[a]	No. (%)
Age, mean (range), y	11 (5-17)
Male patient	79 (57)
Black patient	125 (91)
Annual household income < $30,000/y (n = 127)	87 (69)
Parental education	
Not a high school graduate	42 (30)
High school graduate	43 (31)
Some college	53 (38)
Insurance (n = 136)	
Public	117 (86)
Private or self pay	19 (14)
Total IgE, median (IQR), kU/L (n = 136)	170 (50-450)
Atopic (≥ 1 positive skin test)	124 (90)
Allergy skin testing results	
Cat	89 (64)
Rat	83 (60)
Cockroach	81 (59)
Dust mite	77 (56)
Mouse	71 (51)
Dog	22 (16)
Spirometry,[b] mean (SD)	
FEV_1, % predicted	94.4 (17.7)
FEV_1/FVC %	80.7 (9.6)
Reversible (≥ 12%)	34 (27)
FENO, median (IQR), ppb	32 (16-61)
Use of controller medications for asthma	97 (70)
ED visit in the past 12 mo	111 (80)
Hospitalization in the past 12 mo	26 (19)
ED visit or hospitalization	116 (84)
Maximum symptom days/2 wk,[c] mean ± SD	3.3 ± 4.0
Days of SABA use/2 wk, mean ± SD	4.1 ± 4.9

FENO = fractional exhaled nitric oxide; IQR = interquartile range; ppb = parts per billion; SABA = short-acting β agonist.

[a]n = 138 patients.

[b]Valid data for 126 participants overall and 124 participants for bronchodilator effects.

[c]Maximum days of slowed activity, with exercise-related or nocturnal symptoms.

airborne nicotine concentrations at the baseline home visit. The majority of the population reported taking controller medications for asthma (70%) and most regimens included an inhaled corticosteroid (ICS) (93%). The study population generally had persistent asthma; the mean maximum number of symptom days and days of short-acting β agonist use was at least 3 days per 2 weeks, (mean ± SD, 3.3 ± 4.0 days and 4.1 ± 4.9 days, respectively). The study population had frequent acute health-care use: 19% had been hospitalized, and 80% had an ED visit in the previous year.

Pulmonary physiologic and inflammatory measures were consistent with a population with persistent childhood asthma. Twenty-seven percent had reversible bronchoconstriction, and the mean ± SD prebronchodilator FEV_1/FVC% was 80.7 ± 9.6. The median FENO level was 32 parts per billion (ppb) (interquartile range, 16-61 ppb) and FENO measured during the study demonstrated within- and between-person variability (mean, 43 ppb; between-person SD, 31 ppb; within-person SD, 20 ppb). At baseline, 37% had low FENO levels (< 20 ppb for participants aged < 12 years or < 25 ppb for participants aged ≥ 12 years), 21% had intermediate FENO levels (20-35 ppb for those aged < 12 years or 25-50 ppb for those aged ≥ 12 years), and 42% had high FENO levels (> 35 ppb for those aged < 12 years or > 50 ppb for those aged ≥ 12 years), as defined by the ATS clinical practice guideline.[2] About one-third of the participants changed between these classification categories between any given 3-month follow-up interval.

FENO and Health-care Use

Asthma-related health-care use was common in the study population during the follow-up period. There was a total of 237 acute visits during the follow-up period among 78 subjects, 125 ED visits among 58 subjects, 105 unscheduled doctor visits among 47 subjects, and seven hospitalizations among five subjects. FENO level was not a strong predictor of asthma-related health-care use in the subsequent 3 months, even after adjusting for age, sex, and lung function (Table 2, Fig 1). For example, a twofold increase in FENO level was marginally associated with an 8% increase in the odds of asthma-related, acute health-care use (OR, 1.08; 95% CI, 0.88-1.31).

Using the classification cut points for low, intermediate, and high FENO levels, we determined the negative and positive predictive values (PPV) for future health-care use (Table 3). The PPVs ranged from 0.6% to 32.8% for predicting the need for acute health-care use in the subsequent 3 months. As cut points and definitions of low vs high FENO levels are dependent on age, we stratified by age < 12 years or age ≥ 12 years, and the predictive values did not change substantially (Table 4).

The ATS clinical guideline recommends using change in FENO level to monitor airway inflammation over time in patients with asthma. These recommend applying an algorithm to determine if a patient has had a "significant" increase in FENO level. For example, a change ≥ 20% is considered significant for those with the highest category of inflammation, as is an absolute

Table 2—*Relationship Between FENO and Future, Acute Health-care Encounters*

Acute Health-care Encounter	Crude OR (95% CI)[a]	Adjusted OR (95% CI)
Unscheduled doctor visit	0.94 (0.75-1.18)	0.96 (0.75-1.23)
ED visit	1.03 (0.83-1.27)	1.09 (0.86-1.37)
Hospitalization	2.1 (0.96-4.58)	1.74 (0.77-3.91)
Any acute health-care use	1.07 (0.89-1.28)	1.08 (0.88-1.31)

See Table 1 legend for expansion of abbreviation.

[a]For every twofold increase in FENO level adjusted for baseline age, sex, and FEV_1/FVC.

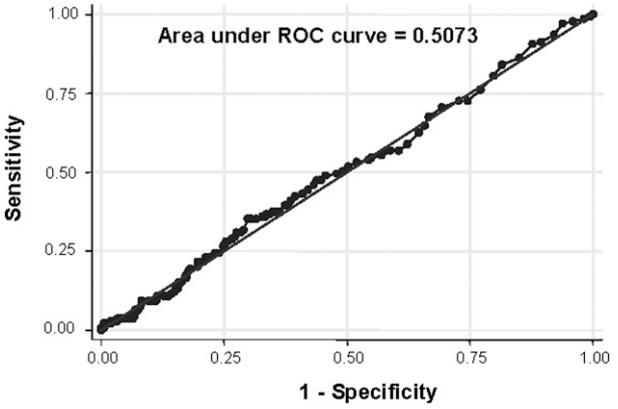

FIGURE 1. ROC curve for the utility of a twofold change in fractional exhaled nitric oxide level in predicting any acute health-care use for asthma. Acute health-care use included hospitalization, ED visit, or unscheduled doctor visit. The area under the curve is 0.5073. ROC = receiver operating characteristic.

change of ≥ 10 ppb for those with lower categories of inflammation. We applied this algorithm, modified for pediatric cut points (if FENO level increased by ≥ 7 ppb for those with FENO values < 35 ppb or ≥ 20% for those with FENO ≥ 35 ppb) and found that a "significant" change in FENO level from the previous visit did not predict future health-care use (Table 5). We also applied these criteria to the change from each participant's mean FENO level, the change from baseline FENO level, and the change from each participant's lowest FENO level, and found that none of these strategies predicted future health-care use.

Lung Function and Health-care Use

Lung function was a better predictor of asthma-related health-care use in the subsequent 3 months than FENO level. In models including $\log_2$(FENO), age, and sex, the strongest association observed was between FEV_1/FVC and future asthma-related, acute health-care use: a 10 percentage-point decrease in FEV_1/FVC was associated with a 32% increase in the odds of future asthma-related, acute health-care use (OR, 1.32; 95% CI, 1.01-1.72) (Table 5). FEV_1 % predicted and forced expiratory flow 25% to 75% were also examined and were not predictors of future asthma-related health-care use. We also tested the hypothesis that the combination of FENO level and FEV_1/FVC ratio would be a better predictor of acute health-care use than FENO level or FEV_1/FVC alone. In models including both $\log_2$(FENO) and FEV_1/FVC, FEV_1/FVC was an independent predictor of future acute health-care use and FENO level was not (Table 6).

DISCUSSION

In a cohort of inner-city, minority children with persistent asthma who were followed for a year, we found that FENO level was not predictive of health-care use for asthma exacerbations. In this population with active asthma, about half of whom required an acute health-care visit during the study period, baseline FENO level, change in FENO level between visits, and thresholds for elevated FENO levels did not identify those at increased risk for an exacerbation requiring an ED visit, a hospitalization, or an unscheduled doctor visit. With the application of ATS-recommended cut points for low, intermediate, and high FENO levels, the predictive value of FENO level in identifying an acute health-care visit was poor, with PPVs of 0.6% to 32.8%. The application of the ATS guideline-recommended algorithm for evaluating clinical change in FENO levels over time did not enhance the ability of FENO level to predict future health-care use for asthma exacerbations.

The negative findings from this study address a research question that must be answered[8]: What is the value of FENO level in managing high-risk symptomatic populations in real world settings? Measurement of FENO as an indicator of pulmonary inflammation is relatively simple and inexpensive compared with other biomarkers, so there is great interest in the potential role for using FENO data in asthma management. FENO level has been shown to correlate with lung function, sputum eosinophil levels, and methacholine responsiveness,[9-17] and, therefore, may provide a noninvasive

Table 3—*Value of FENO in Predicting the Need for Acute Medical Attention for Asthma Over 3 Mo (One Visit)*

	Hospitalization		ED Visit		Unscheduled Doctor Visit		Any Acute Visit	
FENO, ppb	PPV, %	NPV, %	PPV, %	NPV, %	PPV, %	NPV, %	PPV, %	NPV, %
< 20	0.6	98.4	15.7	81.3	20.5	87.0	29.5	71.4
> 35	2.3	99.6	18.5	83.0	14.8	83.8	30.6	72.5
> 50	3.2	99.7	18.5	82.7	14.6	84.0	31.2	72.2
Low[a]	0.5	98.3	16.0	81.3	19.8	87.1	29.4	71.4
High[b]	2.7	99.7	19.4	83.4	16.1	84.7	32.8	73.6

NPV = negative predictive value; PPV = positive predictive value. See Table 1 legend for expansion of other abbreviations.

[a]FENO < 20 ppb for those aged < 12 y and < 25 ppb for those ≥ 12 y.

[b]FENO > 35 ppb for those aged < 12 y and > 50 ppb for those ≥ 12 y.

Table 4—*Value of FENO in Predicting the Need for Acute Medical Attention for Asthma Over 3 Mo (One Visit) Stratified by Age*

	Hospitalization		ED Visit		Unscheduled Doctor Visit		Any Acute Visit	
FENO, ppb	PPV, %	NPV, %	PPV, %	NPV, %	PPV, %	NPV, %	PPV, %	NPV, %
Age < 12 y								
Low[a]	0	100	19.4	77.3	24.3	82.0	33.0	65.3
High[b]	0	100	23.6	80.3	22.6	81.0	39.6	70.1
Age ≥ 12 y								
Low[a]	1.2	96.6	11.9	85.5	14.3	92.4	25.0	77.9
High[b]	6.2	99.3	13.6	86.5	7.4	88.5	23.5	77.0

See Table 1 and 3 legends for expansion of abbreviations.
[a]FENO < 20 ppb for those aged < 12 y and < 25 ppb for those ≥ 12 y.
[b]FENO > 35 ppb for those aged < 12 y and > 50 ppb for those ≥ 12 y.

means to predict clinical deterioration or improvement beyond the traditionally available tests in a subspecialty office setting. However, our results suggest that FENO level is not a useful clinical tool for identifying children who will have asthma exacerbations that require health-care visits among high-risk urban populations.

Clinical practice guidelines for use of FENO levels provide recommendations graded by the strength of the recommendation and weight of the supporting evidence. The guidelines support the use of FENO level in asthma with a strong recommendation despite low-quality supporting evidence. Specifically, clinical trials have been conducted in adults[18,19] and in children and adolescents[1,20-22] with equivocal results about the utility of FENO data in tailoring asthma therapy. Although clinical trials that investigate algorithm-based interventions may be subject to methodological concerns,[22,23] a meta-analysis of these trials concluded that tailoring the dose of ICSs based on FENO level did not significantly reduce exacerbations or improve FEV_1 or asthma symptoms.[24] While the trials used different approaches to tailor ICS therapy, the adult studies had a reduction in the ICS final dose in the FENO group while the child and adolescent studies resulted in higher ICS doses in the groups assigned to FENO-based management.

It is possible that the utility of FENO measurement varies during different developmental stages. Studies in preschool children have suggested that FENO testing may be a beneficial tool predicting future asthma.[25-29] Debley et al[26] found FENO level to be predictive of changes in lung function and risk of future wheezing, suggesting a role for prediction of future asthma in infants and toddlers. A large cohort study in The Netherlands also suggested that FENO measured before the age of 4 years was predictive of wheeze up to age 8.[25] However, these studies investigated the use of baseline values of FENO to predict the persistence of asthma beyond early childhood rather than exacerbations in populations with established disease. In addition, these studies do not shed light on the potential application of FENO testing at regular intervals that might approximate real-time use of testing in clinical settings.

While studies in adults might be slightly more encouraging,[10,24,30] studies in school-age children have not strongly supported the use of FENO data in asthma management.[1,20,24,31-33] A large clinical trial of inner-city adolescents with asthma found that adding FENO level as an indicator of asthma control resulted in higher doses of ICS without clinical benefit.[1] The present

Table 5—*Application of ATS Guideline Algorithm[a] for Significant Increase in FENO*

Acute Health-care Encounter	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Unscheduled doctor visit	0.97 (0.58-1.63)	1.02 (0.59-1.76)
ED visit	1.26 (0.78-2.04)	1.25 (0.75-2.08)
Hospitalization	0.57 (0.07-4.76)	0.67 (0.07-6.15)
Any acute health-care use	1.12 (0.74-1.67)	1.11 (0.72-1.72)

ATS = American Thoracic Society. See Table 1 legend for expansion of other abbreviations.
[a]For every significant increase between consecutive FENO measurements over 3-mo intervals, defined as FENO level increased by > 7 ppb for values < 35 ppb or > 20% for FENO ≥ 35 ppb for those aged < 12 y and FENO level increased by > 10 ppb for values < 50 ppb or > 20% for FENO level ≥ 50 ppb for those aged ≥ 12 y.
[b]Adjusted for baseline age, sex, and FEV_1/FVC ratio.

Table 6—*Relationship Between Lung Function[a] and Future, Acute Health-care Encounters*

Acute Health-care Encounter	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Unscheduled doctor visit	0.91 (0.66-1.27)	0.95 (0.68-1.32)
ED visit	1.23 (0.92-1.64)	1.34 (0.98-1.83)
Hospitalization	3.01 (1.32-6.88)	2.23 (0.84-5.86)
Any acute health-care use	1.23 (0.96-1.58)	1.32 (1.01-1.72)

See Table 1 legend for expansion of abbreviation.
[a]As measured by FEV_1/FVC ratio.
[b]For every 10 percentage-point decrease in FEV_1/FVC %.
[c]Adjusted for base age, sex, and $\log_2$FENO.

cohort study of urban children with moderate to severe asthma extends these findings by providing an opportunity to study a similar high-risk population receiving usual care. Similar to previous studies, FENO level had little predictive value for identifying future asthma exacerbations that required an acute-care visit even in a study population receiving usual care.

As our study population was highly atopic, with 90% of children with at least one positive skin test, one might expect that a marker of eosinophilic inflammation, such as FENO level, would have been a better predictor of asthma exacerbations. A potential explanation for the lack of predictive value of FENO level in the present study is that triggers for acute care visits may have exacerbated asthma through noneosinophilic pathways. Alternate explanations might include lack of precision in the measurement of FENO that attenuated the relationship between FENO level and risk of acute visits, or a weaker correlation between FENO level and eosinophilic inflammation compared with what has been previously reported. These are less likely given prior studies that demonstrate reproducibility of FENO measurements[34,35] and the strong, existing evidence of correlation between eosinophilic airway inflammation and FENO level.[9,11,13-17]

There were limitations to the study design that warrant consideration. As our study population was limited to children in Baltimore City, results may not be generalizable to other populations. In many of the clinical trials that have evaluated the predictive value of FENO level, measurements occurred on a weekly basis for a period of several weeks. It is possible that increases in FENO level preceding an exacerbation were not captured due to the 3-month interval between measurements. However, in a sensitivity analysis, we found the predictive value of FENO level did not improve when we restricted the analysis to acute health use in the 1-month period following FENO measurement. It would be of interest to investigate the effect of individual patient characteristics, such as ICS use and secondhand smoke exposure, on the predictive value of FENO level. While we did not find evidence that these factors modified the predictive value of FENO level, our sample size was not large enough to draw definitive conclusions about the influence of individual patient characteristics. It is possible that our findings that FENO level has little predictive value in identifying future health-care use were attributable to a lack of power. Although a larger sample size may have resulted in more statistically significant results, it would not be expected to increase the magnitude of the association between FENO level and future health-care use. In addition, the sample size of 138 inner-city children with asthma that undergo clinic visits with FENO testing every 3 months is representative of a sample that can be found in many pulmonary, allergy, and pediatric clinics across the country, and the quarterly clinic visits reflect real-world practice patterns. The inability to use FENO level to predict the need for acute health-care visits in this setting has meaningful clinical implications.

While guidelines support the use of FENO data in asthma management, FENO level was not predictive of asthma exacerbations requiring acute-care visits among a high-risk cohort of urban children with asthma. Application of the suggested cut points and the recommended algorithm for evaluating change in FENO level over time did not enhance the predictive value of FENO levels. While these results may not be applicable to other populations across the entire spectrum of age, our findings suggest that the utility of FENO levels may be limited in this high-risk population and further evidence is needed to support the current recommendations for implementing FENO measurement into routine asthma management.

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Ms Curtin-Brosnan: contributed to the analysis and interpretation of the data and the drafting and critical review of the manuscript and has seen and approved the final version.
Dr Diette: contributed to the study design, analysis and interpretation of the data, and the drafting and critical review of the manuscript and has seen and approved the final version.
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REFERENCES

1. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet*. 2008;372(9643):1065-1072.
2. Dweik RA, Boggs PB, Erzurum SC, et al; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide

Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602-615.
3. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179-187.
4. Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005; 26(2):319-338.
5. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912-930.
6. American Thoracic Society. Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 1999; 160(6):2104-2117.
7. Morgan WJ, Crain EF, Gruchalla RS, et al; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. 2004;351(11):1068-1080.
8. Kharitonov SA, Barnes PJ. Does exhaled nitric oxide reflect asthma control? Yes, it does! *Am J Respir Crit Care Med*. 2001;164(5):727-728.
9. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax*. 1998;53(2):91-95.
10. Jones SL, Kittelson J, Cowan JO, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med*. 2001;164(5): 738-743.
11. Mattes J, Storm van's Gravesande K, Reining U, et al. NO in exhaled air is correlated with markers of eosinophilic airway inflammation in corticosteroid-dependent childhood asthma. *Eur Respir J*. 1999;13(6):1391-1395.
12. Zacharasiewicz A, Wilson N, Lex C, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med*. 2005; 171(10):1077-1082.
13. Warke TJ, Fitch PS, Brown V, et al. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax*. 2002;57(5):383-387.
14. Piacentini GL, Bodini A, Costella S, et al. Exhaled nitric oxide and sputum eosinophil markers of inflammation in asthmatic children. *Eur Respir J*. 1999;13(6):1386-1390.
15. Piacentini GL, Bodini A, Costella S, et al. Exhaled nitric oxide, serum ECP and airway responsiveness in mild asthmatic children. *Eur Respir J*. 2000;15(5):839-843.
16. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med*. 2001;164(8 pt 1):1376-1381.
17. Berlyne GS, Parameswaran K, Kamada D, Efthimiadis A, Hargreave FE. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. *J Allergy Clin Immunol*. 2000;106(4):638-644.
18. Shaw DE, Berry MA, Thomas M, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;176(3):231-237.
19. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med*. 2005;352(21):2163-2173.
20. de Jongste JC, Carraro S, Hop WC, Baraldi E; CHARISM Study Group. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med*. 2009;179(2):93-97.
21. Pijnenburg MW, Bakker EM, Lever S, Hop WC, De Jongste JC. High fractional concentration of nitric oxide in exhaled air despite steroid treatment in asthmatic children. *Clin Exp Allergy*. 2005;35(7):920-925.
22. Fritsch M, Uxa S, Horak F Jr, et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol*. 2006;41(9):855-862.
23. Gibson PG. Using fractional exhaled nitric oxide to guide asthma therapy: design and methodological issues for ASthma TReatment ALgorithm studies. *Clin Exp Allergy*. 2009;39(4): 478-490.
24. Petsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev*. 2009;(4):CD006340.
25. Caudri D, Wijga AH, Hoekstra MO, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax*. 2010;65(9):801-807.
26. Debley JS, Stamey DC, Cochrane ES, Gama KL, Redding GJ. Exhaled nitric oxide, lung function, and exacerbations in wheezy infants and toddlers. *J Allergy Clin Immunol*. 2010; 125(6):1228-1234.
27. Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. *Thorax*. 2003;58(6): 494-499.
28. Moeller A, Diefenbacher C, Lehmann A, et al. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. *J Allergy Clin Immunol*. 2008; 121(3):705-709.
29. Beigelman A, Mauger DT, Phillips BR, et al; Childhood Asthma Research and Education (CARE) Network; National Heart, Lung and Blood Institute. Effect of elevated exhaled nitric oxide levels on the risk of respiratory tract illness in preschool-aged children with moderate-to-severe intermittent wheezing. *Ann Allergy Asthma Immunol*. 2009;103(2): 108-113.
30. Pérez-de-Llano LA, Carballada F, Castro Añón O, et al. Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma. *Eur Respir J*. 2010;35(6):1221-1227.
31. Cabral AL, Vollmer WM, Barbirotto RM, Martins MA. Exhaled nitric oxide as a predictor of exacerbation in children with moderate-to-severe asthma: a prospective, 5-month study. *Ann Allergy Asthma Immunol*. 2009;103(3):206-211.
32. Carrà S, Gagliardi L, Zanconato S, et al. Budesonide but not nedocromil sodium reduces exhaled nitric oxide levels in asthmatic children. *Respir Med*. 2001;95(9):734-739.
33. Paro-Heitor ML, Bussamra MH, Saraiva-Romanholo BM, Martins MA, Okay TS, Rodrigues JC. Exhaled nitric oxide for monitoring childhood asthma inflammation compared to sputum analysis, serum interleukins and pulmonary function. *Pediatr Pulmonol*. 2008;43(2):134-141.
34. Napier E, Turner SW. Methodological issues related to exhaled nitric oxide measurement in children aged four to six years. *Pediatr Pulmonol*. 2005;40(2):97-104.
35. Schiller B, Hammer J, Barben J, Trachsel D. Comparability of a hand-held nitric oxide analyser with online and offline chemiluminescence-based nitric oxide measurement. *Pediatr Allergy Immunol*. 2009;20(7):679-685.