Clinical Communications

Exhaled nitric oxide is associated with severity of pediatric acute asthma exacerbations

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Clinical Implication

- Fractional excretion of nitric oxide is associated with acute pediatric asthma exacerbation severity as measured by % predicted FEV_1 and is greater in African American patients in comparison with white pediatric patients during exacerbations. Knowledge of these associations might inform the use of fractional excretion of nitric oxide before and during acute asthma exacerbations in children.

TO THE EDITOR:

There is limited information about the role of fractional excretion of nitric oxide (FeNO) during pediatric acute asthma exacerbations.[1,2] We performed a secondary analysis of data from a prospective cohort of participants ages 5 to 17 years old. The participants had physician-diagnosed asthma and presented to our tertiary pediatric emergency department with acute exacerbations defined by using National Asthma Education and Prevention Program guidelines that required inhaled bronchodilator and systemic corticosteroid treatment.[3] We sought to examine whether there are associations of FeNO with % predicted FEV_1 and with relevant patient characteristics during these episodes.[4] Prebronchodilator pulmonary examination, FeNO testing, and spirometry for % predicted FEV_1 were performed under an institutional review board exemption for immediate informed consent. FeNO testing was performed before spirometry to avoid alterations of airway tone from forced vital capacity maneuvers that may, in turn, influence measured airway FeNO.[4] Written informed parental consent and participant assent were then obtained, and inhaled bronchodilator treatment was administered. The clinical team directed all patient management and was blinded to test results.

Demographic information was recorded, and asthma severity variables determined for each participant included expiratory-phase prolongation, air entry, wheezing, accessory muscle use, and oxyhemoglobin saturation by pulse oximetry on room air. These variables were used to electronically calculate the acute asthma intensity research score (AAIRS) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), a validated bedside severity score.[5]

We measured the primary explanatory variable, FeNO, by using a Niox MINO (Aerocrine, Solna, Sweden) hand-held analyzer. Visual and auditory feedback from the device assisted the participants in maintaining a steady exhalation. The device provided confirmation of an expiratory maneuver of sufficient quality for valid FeNO output. One validated expiratory measurement was accepted because participants were then asked to perform spirometry before receiving expeditious bronchodilator

TABLE I. Univariate associations of FeNO with demographic and asthma characteristics among 436 participants ages 5-17 years with acute asthma exacerbations

Patient characteristic	FeNO (ppb), median (IQR)	*P* value
Demographic variables		
Sex		.36
Girls (n = 175)	36 (19-62)	
Boys (n = 261)	42 (22-64)	
Race		<.001
African American (n = 244)	45 (26-75)	
White (n = 191)	32 (16-54)	
Smoke exposure in primary residence		.73
Yes (n = 173)	41 (20-65)	
No (n = 263)	38 (21-62)	
Upper respiratory symptoms		.21
Yes (n = 156)	36 (20-56)	
No (n = 280)	41 (21-68)	
Season of emergency department visit		.08
Sep-Nov (n = 138)	41 (20-74)	
Dec-Feb (n = 94)	32 (16-52)	
Mar-May (n = 113)	39 (23-64)	
Jun-Aug (n = 91)	42 (24-64)	
Asthma severity variables		
Current medication use		
Inhaled corticosteroid		.14
Yes (n = 181)	36 (20-59)	
No (n = 255)	41 (22-66)	
Acute course of systemic CCS		.071
Yes (n = 104)	32 (16-62)	
No (n = 332)	41 (23-65)	
Chronic use of systemic CCS		.31
Yes (n = 17)	35 (19-47)	
No (n = 418)	40 (21-64)	
Leukotriene receptor antagonists		.16
Yes (n = 128)	36 (19-58)	
No (n = 308)	40 (22-66)	
Expiratory phase		<.001
Normal (n = 235)	32 (16-56)	
Prolonged (n = 189)	47 (28-69)	
Severely prolonged (n = 12)	56 (44-100)	
Air entry		<.001
Normal (n = 202)	30 (16-57)	
Decreased (n = 222)	46 (25-68)	
Severely decreased (n = 12)	51 (46-83)	
Wheeze		<.001
None (n = 112)	24 (12-47)	
Expiratory (n = 142)	35 (22-64)	
Inspiratory and expiratory (n = 182)	49 (30-70)	
Sternocleidomastoid retractions		<.001
Yes (n = 192)	48 (30-73)	
No (n = 244)	32 (17-55)	
Intercostal retractions		.088
Yes (n = 42)	48 (29-76)	
No (n = 394)	39 (20-63)	
Subcostal retractions		.008
Yes (n = 48)	50 (34-79)	
No (n = 388)	36 (20-62)	

CCS, corticosteroid; *FeNO*, fractional excretion of nitric oxide; *IQR*, interquartile range.

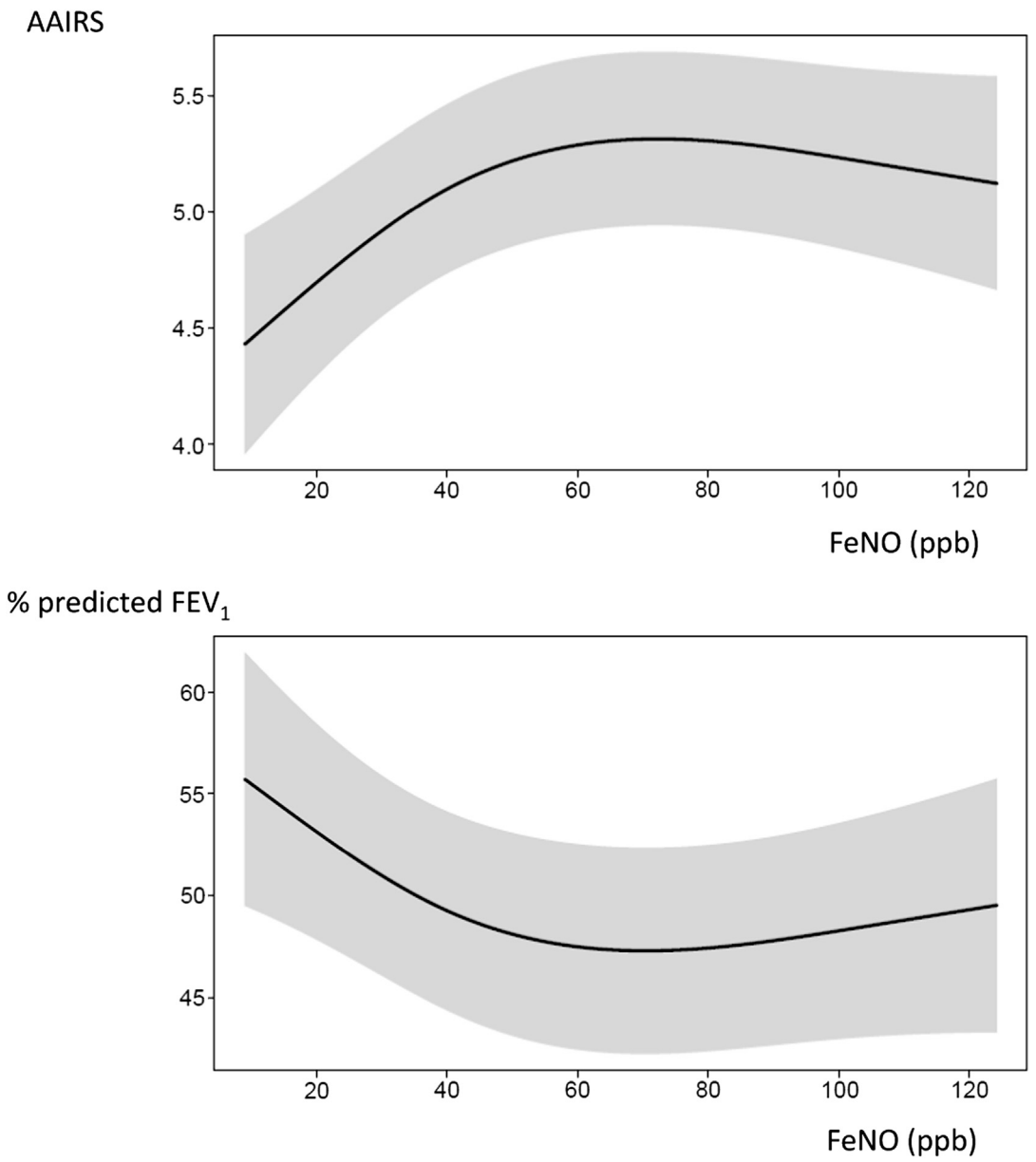

FIGURE 1. Association between fractional excretion of nitric oxide (FeNO, x-axis) with the acute asthma intensity research score (AAIRS, *upper panel*) and with % predicted FEV_1, *lower panel*. The plots depict a smooth adjusted association derived from multivariable regression models that included the covariates, age, sex, body mass index, asthma severity score, albuterol, and inhaled and oral corticosteroid use.

and corticosteroid treatment. The primary response variable was % predicted FEV_1 by spirometry. Spirometry was recorded when a participant was able to perform a minimum of 3 forced airway maneuvers in accordance with American Thoracic Society quality criteria.[6] Secondary outcomes included the AAIRS and the participant demographic and asthma characteristics. To assess for associations of FeNO with % predicted FEV_1 and the AAIRS, we used separate multivariable regression models adjusted for age, race, sex, body mass index, and current use of inhaled albuterol, inhaled corticosterid and acute oral corticosteroids. FeNO was included as a flexible nonlinear term by using restricted cubic spline techniques.[7] Statistical analyses were performed by using R version 3.0.1 (http://www.r-project.org).

Between April 2008 and February 2013, 806 unique participants were enrolled, and 436 (54%) were able to perform FeNO measurement, with median (interquartile range [IQR]) FeNO 39 ppb (21-64 ppb), AAIRS 5 (2-8), and % predicted FEV_1 51 (36-73). Demographic and asthma characteristics are displayed in Table E2 (in this article's Online Repository at www.jaci-inpractice.org), and univariate associations in Table I. Higher FeNO levels were associated with most asthma severity variables and with African American (median [IQR], 45 ppb [I26-75 ppb]) compared with white race (median [IQR], 32 ppb [16-54 ppb], $P = .001$) (Table I).

In the primary multivariable regression model, FeNO was associated with % predicted FEV_1 ($P < .018$), after adjustment for

the covariates listed above. The plot derived from this model is presented in Figure 1 and depicts a smooth adjusted association. A 43 ppb increase of FeNO (25th-75th percentile [21-64 ppb]) was associated with an increased % predicted FEV_1 (ß-coefficient, −5.5% [95% CI, −1.7 to −9.4]). This association appeared curvilinear and leveled off at approximately 65 ppb (the 75th percentile) and higher. FeNO also was associated with the AAIRS ($P < .001$), although the change of AAIRS was not clinically meaningful (ß-coefficient 0.58 [95% CI, 0.30-0.87]). In a multivariable model with FeNO as the response variable, there was an association of African American race with FeNO after adjustment for baseline AAIRS, age, sex, body mass index, second-hand smoke exposure, and current use of inhaled albuterol, inhaled corticosteroids, acute or chronic oral corticosteroids, and leukotriene antagonist (ß-coefficient 13.0 [95% CI, 6.1-19.9]).

Analysis of our results suggests that FeNO measured before treatment for children with acute asthma exacerbations is associated with % predicted FEV_1. To our knowledge, a positive correlation between FeNO and % predicted FEV_1 during pediatric acute asthma exacerbations has not been previously reported. At levels of FeNO above approximately 65 ppb (75th percentile), this association appears to level off, which may indicate that further increases in eosinophilic airway inflammation have a minimal association with lung function measured by using % predicted FEV_1. Further study is needed to determine whether serial measurement of FeNO predicts an impending acute exacerbation or makes possible interventions to prevent this progression. We also found that African American children have significantly higher FeNO levels during acute asthma exacerbations than white children. Although a racial difference in baseline FeNO levels has been previously reported, to our knowledge, this is the first report of a difference during acute exacerbations.[8,9] Further studies that examine these differences during and after treatment of acute exacerbations according to race may help individualize treatment plans.

Our study has limitations. First, we obtained a single FeNO measurement for each participant, a decision made due to the short period of time available for study measurements and the need for emergent therapeutic intervention. Although this may limit test reproducibility, the FeNO analyzer provides confirmation of an expiratory maneuver of sufficient quality for valid FeNO output. Second, the study was conducted at a single center, and this may limit external validity. Third, in addition to upper respiratory tract infection and second-hand smoke exposure, there are other variables that affect FeNO levels that could confound our results, such as recent food intake, fever, allergic rhinitis, exercise, and other underlying diseases. Fourth, although we did obtain FeNO measurements before any treatment administered in the emergency department, many participants were already using albuterol, inhaled corticosteroid, and leukotriene antagonists at baseline or as acute therapy. However, we adjusted for these variables in multivariable analyses. In summary, we found associations of FeNO with % predicted FEV_1 and with African American race. Knowledge of these associations might inform the use of FeNO before and during acute asthma exacerbations in children, a population in which there are limited objective measures of severity available at the bedside.

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TABLE E1. Acute asthma intensity research score (AAIRS) components*

	Component value			
Component	**0**	**1**	**2**	**3**
Retractions				
Sternocleidomastoid	No		Yes	
Intercostal	No		Yes	
Subcostal	No		Yes	
Air entry	Normal	Decreased at bases	Widespread decrease	Absent or minimal
Wheezing	Absent	Expiratory	Inspiratory and expiratory	Audible without stethoscope or silent chest
SpO_2	>95%	92%-94%	<92%	
Expiratory phase	Normal	Prolonged	Severely prolonged	

SpO_2, oxyhemoglobin saturation by pulse oximetry.
*Severity categories by AAIRS: mild, 1-6; moderate, 7-11; severe, 12-16.

TABLE E2. Demographic and asthma severity variables of participants ages 5-17 years old with acute asthma exacerbations

	FeNO measurement availability		
	Yes (n = 436)	**No (n = 370)**	**Overall cohort (n = 806)**
Demographic variable			
Age (y), median (IQR)	9.0 (7.0-12.0)	7.0 (5.0-9.0)	8.0 (6.0-11.0)
Boys, no. (%)	261 (60)	234 (63)	495 (61)
Race or ethnicity, no. (%)			
African American	244 (56)	218 (59)	462 (57)
White	191 (44)	146 (39)	337 (42)
Asian	1 (0)	5 (1)	6 (1)
American Indian/Alaskan	0 (0)	1 (0)	1 (0)
Hispanic	28 (6)	30 (8)	58 (7)
Body mass index (kg/m^2), median (IQR)	18.8 (16.2-22.5)	16.7 (15.3-19.8)	17.9 (15.5-21.8)
Type of insurance, no. (%)			
Commercial	174 (40)	132 (36)	306 (38)
TennCare/Medicaid	254 (58)	233 (63)	487 (60)
None	8 (2)	5 (1)	13 (2)
Second-hand smoke exposure in primary residence, no. (%)	173 (40)	128 (35)	301 (37)
Participant smokes cigarettes, no. (%)	6 (1)	1 (0)	7 (1)
Current upper respiratory infection symptoms, no. (%)	156 (36)	156 (42)	312 (39)
AAIRS, median (IQR)	3 (1-6)	6 (3-9)	5 (2-8)
% predicted FEV_1, median (IQR), (n = 463)*	56 (40-76)	42 (32-61)	51 (36-73)
Asthma severity variable			
Medications in use, no. (%)			
Inhaled albuterol	356 (82)	310 (84)	666 (83)
Inhaled corticosteroid	181 (42)	162 (44)	343 (43)
Acute course of systemic corticosteroid	104 (24)	88 (24)	192 (24)
Leukotriene receptor antagonist	94 (25)	128 (29)	222 (28)
Chronic systemic corticosteroid	17 (4)	6 (2)	23 (3)
GINA control variables, no. (%)			
Daytime symptoms >2 times per wk	206 (47)	171 (46)	377 (47)
Nighttime symptoms ≥1 time per wk	239 (55)	197 (53)	436 (54)
Limitation of activity	226 (52)	165 (45)	391 (49)
Rescue treatment ≥2 times per wk	207 (47)	158 (43)	365 (45)
History of intensive care admission, no. (%)	88 (20)	65 (18)	153 (19)

AAIRS, Acute asthma intensity research score; *FeNO,* fractional excretion of nitric oxide; *GINA,* Global Initiative for Asthma; *IQR,* interquartile range.
*A total of 463 participants (60%) provided American Thoracic Society-criteria spirometry for % predicted FEV_1.