

PHENOTYPES AND DIAGNOSIS

Noninvasive Testing of Lung Function and Inflammation in Pediatric Patients with Acute Asthma Exacerbations

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Objective. There is limited information on performance rates for tests of lung function and inflammation in pediatric patients with acute asthma exacerbations. We sought to examine how frequently pediatric patients with acute asthma exacerbations could perform noninvasive lung function and exhaled nitric oxide (FE_{NO}) testing and participant characteristics associated with successful performance. **Methods.** We studied a prospective convenience sample aged 5–17 years with acute asthma exacerbations in a pediatric emergency department. Participants attempted spirometry for percent predicted forced expiratory volume in 1 second (%FEV₁), airway resistance (Rint), and FE_{NO} testing before treatment. We examined overall performance rates and the associations of age, gender, race, and baseline acute asthma severity score with successful test performance. **Results.** Among 573 participants, age was (median [interquartile range]) 8.8 [6.8, 11.5] years, 60% were male, 57% were African-American, and 58% had Medicaid insurance. Tests were performed successfully by the following [*n* (%)]: full American Thoracic Society–European Respiratory Society criteria spirometry, 331 (58%); Rint, 561 (98%); and FE_{NO}, 354 (70% of 505 attempted test). Sixty percent with mild–moderate exacerbations performed spirometry compared to 17% with severe exacerbations (*p* = .0001). Participants aged 8–12 years (67%) were more likely to perform spirometry than those aged 5–7 years (48%) (OR = 2.23, 95% CI: 1.45–3.11) or 13–17 years (58%) (OR = 1.61, 95% CI: 1.00–2.59). **Conclusions.** There is clinically important variability in performance of these tests during acute asthma exacerbations. The proportion of patients with severe exacerbations able to perform spirometry (17%) limits its utility. Almost all children with acute asthma can perform Rint testing, and further development and validation of this technology is warranted.

Keywords airway resistance, asthma, asthma exacerbation, lung function testing, spirometry

INTRODUCTION

Asthma is the most common chronic disease of childhood and the most frequent reason for childhood hospitalization in the United States (1, 2, 3). Acute exacerbations account for almost 2 million emergency department (ED) admissions annually and an ED relapse rate of 7–15% (4).

This complex genetic and environmental disease has great variability of clinical expression and response to treatment, and clinical evaluation can be difficult (5). There are few objective measures to assess exacerbation severity, and these are infrequently available in the ED environment. Acute severity scores may not correlate with the degree of functional lung impairment in pediatric patients with acute asthma exacerbations (6). As a result, there is variability in diagnosis and management and a lack of objective testing available to assess severity and response to treatment (7).

Objective measurements of airflow obstruction (forced expiratory volume in 1 second, %FEV₁), airway resistance (Rint), and airway inflammation (exhaled nitric

oxide, FE_{NO}) have the potential to decrease this variability and to facilitate appropriate care of the pediatric patient with an acute asthma exacerbation. However, there is limited information on performance rates and patient characteristics associated with successful performance for these noninvasive measures (6, 8–10). Becker and colleagues and Kerem and colleagues enrolled only participants who could perform spirometry (6, 8). Langan and Spiro examined performance rates for spirometry, defined as two acceptable forced vital capacity (FVC) maneuvers, among 36 children above 6 years of age with asthma exacerbations and found a 91% success rate (10). We are not aware of studies examining Rint during acute asthma exacerbations in pediatric patients. Kwok and colleagues achieved a performance rate of 68% for FE_{NO} measurement among participants aged 2–18 years with acute asthma exacerbations (11).

Our primary objective was to determine how frequently measurement of %FEV₁, Rint, and FE_{NO} could be successfully performed in patients aged 5–17 years with acute asthma exacerbations. We also examined associations of *a priori* designated participant characteristics (age, gender, race, and baseline acute asthma severity score) with successful test performance and the values of test measurements.

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METHODS

Study Design, Setting, and Selection of Participants

This observational study included 573 consecutive, unique participants enrolled in a parent study, the Acute Asthma Severity Assessment Protocol (AASAP) (12). AASAP is an ongoing prospective study of children aged 5–17 years with acute asthma exacerbations who present to an urban, academic pediatric ED (PED). Inclusion criteria were age 5–17 years, doctor-diagnosed asthma, signs or symptoms of an asthma exacerbation (cough, dyspnea, wheezing, and/or chest pain) (13), need for treatment with systemic corticosteroid (CCS) and inhaled bronchodilator as determined by the attending physician, and availability for phone follow-up (an AASAP requirement). We excluded participants with chronic lung disease other than asthma, foreign body aspiration, or other reasons for pertinent signs and symptoms. The Institutional Review Board reviewed and approved this study protocol (#080058). Written informed consent of the parent and assent of the participant were obtained. The clinical team was not aware of test values and made all management decisions.

Methods of Measurement

At baseline, defined as after triage but before systemic CCS treatment, we recorded medical, family, and social history and Global Initiative for Asthma (GINA) chronic asthma control for the preceding 3 months (14). Other variables measured at baseline included the degree of breathlessness as determined by the ability to speak (complete, short or partial sentences, words, or no speech) and the Pediatric Asthma Score (PAS, Table 1). The 15-point PAS was developed from expert consensus asthma management guidelines and has been used for approximately 15 years in our PED as the primary bedside measure to assess acute asthma severity (15, 16). The principal investigator (DHA) and research assistant (DJR) were trained by the device manufacturers and pediatric pulmonary function technicians in test performance.

Explanatory and Outcome Measures

Explanatory variables used to examine the associations of participant characteristics with successful test performance were determined *a priori* and included age, gender, race, and baseline PAS. We chose these variables because they are biologically plausible and readily obtained in all participants. The outcomes of these analyses were the ability of the participants to perform standardized Rint, FE_{NO}, and spirometry tests.

Airway Resistance. Rint was measured using a MicroDirect MRT6000 module (Micro Medical, Kent, England). A nose clip was applied and the participant was instructed to perform comfortable, tidal volume breathing through the mouthpiece (SpiroSafe, Micro Medical) and to keep the tongue against the floor of the mouth. We supported the submental tissue and cheeks and extended the neck slightly to achieve the “sniffing” position (17). Five measurements were made during exhalation and the median value recorded. The device outputs percent predicted values for participants aged 2–10 years using the McKenzie standards and absolute values (kPa/l/sec) for participants 11 years of age and above (18).

Exhaled Nitric Oxide. FE_{NO}, a measure of airway inflammation, was measured using a NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). We instructed the participant to inhale through the device mouthpiece from residual volume to total lung capacity and then to exhale through the device at a steady flow rate. The device outputs user feedback with audible and light signals to enable the participant to exhale at an appropriate and steady flow rate (19). This prevents contamination with nasal air by closing the velum. Measurement was made from a 6-sec exhalation time (20). Rint and FE_{NO} were measured before spirometry because the FVC maneuvers required for spirometry may alter airway tone and Rint measures (21). The Rint and FE_{NO} measurement devices output results only after valid measurement maneuvers.

TABLE 1.—Asthma severity score in use during the study period.

Score component		Value observed for score component			
Respiratory rate by age (years)					
2–3	18–26	27–34	35–39	≥40	
4–5	16–24	25–30	31–35	≥36	
6–12	14–20	21–26	27–30	≥31	
> 12					
SpO ₂	>98% ^a	95–97% ^a	90–94% ^a	<90% ^b	
Auscultation	Normal breath sounds with good aeration throughout	End expiratory wheezes only	Expiratory wheezing	Inspiratory and expiratory wheezing or diminished breath sounds	
Retractions	None	Intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular	
Dyspnea	Speaks in complete sentences	Speaks in short sentences, coos and babbles	Speaks in partial sentences, short cry	Speaks in single words or short phrases/grunting	
Scoring value	0	1	2	3	

Note: Asthma severity (total score): normal (0–4); mild (5–7); moderate (8–11); severe (12–15).

^aOn room air.

^bOn room air or oxygen.

Spirometry. Spirometry was performed using a MicroDirect MicroLoop spirometer (Micro Medical, Kent, England). The spirometer was calibrated each morning with a 3-l syringe. A nose clip was applied and the participant performed FVC maneuvers in accordance with American Thoracic Society–European Respiratory Society (ATS/ERS) 2005 spirometry standards (22, 23). Knudson standards were used to calculate %FEV₁ (24, 25).

For each participant, we attempted to obtain three FVC maneuvers meeting ATS/ERS acceptability criteria (22, 23). These include reproducibility criteria but note that “use of data from maneuvers with poor reproducibility is left to the discretion of the interpreter.” This is because patients with airways obstruction may have greater coefficients of variation and may not meet full reproducibility criteria (26). Eliminating trials from these participants may result in systematic bias in the results reported.

Therefore, for participants who could not perform three FVC maneuvers that met full ATS/ERS criteria but who had at least one maneuver with flow–volume and volume–time curves meeting ATS/ERS criteria for start-of-test and end-of-test, a standing pulmonary function test oversight committee reviewed these trials to determine whether the results were “high quality.” This committee is composed of a pediatric pulmonary function technician and a pulmonologist–pulmonary physiologist. Each member recorded their determination whether a non-ATS/ERS trial was high quality based on the flow–volume and volume–time curves and spirometry calculations of the available FVC maneuvers. Each member was blinded to the other member’s determination and to all other participant data. A trial was designated high quality if both members made this assessment independently.

Statistical Analysis

We included only first enrollment data for all analyses for participants with duplicate enrollments. Continuous variables are reported as means (standard deviation, SD)

or medians [interquartile range (IQR)], as appropriate, and categorical variables as frequencies and proportions. Race and ethnicity were categorized in accordance with National Institutes of Health (NIH) guidelines (27). We compared demographic characteristics of study participants with those of all patients aged 5–17 years admitted to the PED with a primary diagnosis of asthma exacerbation (ICD code 493). The chi-square (χ^2) test was used to examine differences in test performance proportions by age and by asthma severity groups. We used separate multivariable logistic regression models to assess the independent associations of the *a priori*-determined predictor variables (age, gender, race, and baseline PAS) with performance of Rint, full ATS/ERS criteria spirometry, and FE_{NO} testing. To allow the testing of nonlinear relationships of age with the ability to perform each test, age was included as a flexible term using restricted cubic splines (28). We also provide analyses for age groups (5–7, 8–12, and 13–17 years) based on mid- and late-childhood and adolescence, and for asthma severity (mild, moderate, and severe). All analyses were performed using R version 2.10.1 software (29).

RESULTS

Among 662 eligible patients approached for enrollment during the period 7 April 2008 to 30 June 2010, 640 provided informed consent and were enrolled, and 1 could not be contacted for phone follow-up (an AASAP exclusion criterion), resulting in 639 participants with data available (Figure 1). Sixty-five patients had duplicate enrollments in this study during subsequent PED admissions. After excluding these, data from 573 unique participant enrollments were included for analyses.

The demographic characteristics of the participants were similar to those of the population aged 5–17 years admitted to the PED with a final diagnosis of acute asthma exacerbation (Table 2). Age (median [IQR]) of the participants was 8.8 [6.8, 11.5], 60% were male and 57% African-American, 58% had Medicaid insurance,

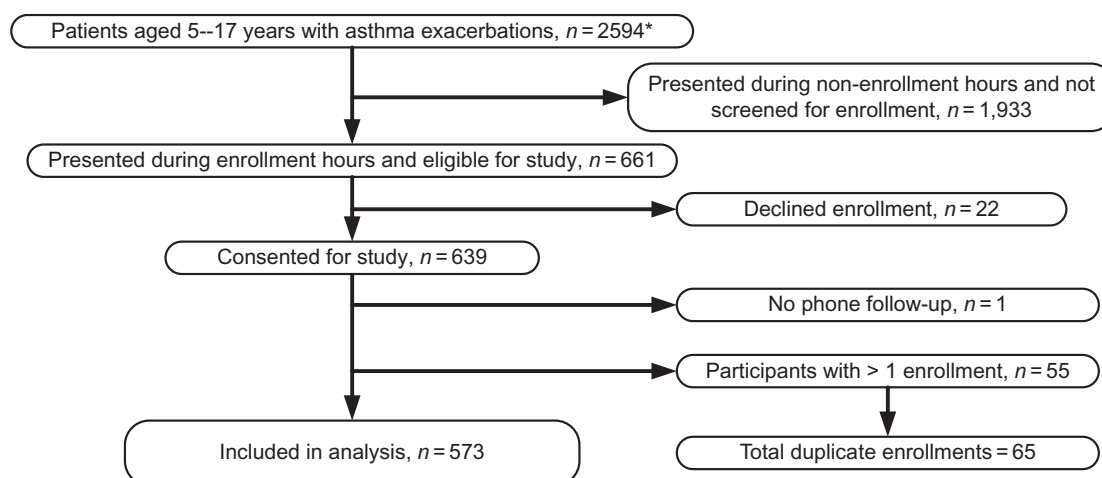


FIGURE 1.—Participant recruitment and study implementation. *Overall population of patients presenting to pediatric emergency department during study period with final diagnosis of asthma exacerbation.

TABLE 2.—Baseline demographic and asthma characteristics of participants with acute asthma exacerbations and of population aged 5–17 years with acute asthma admitted to pediatric emergency department during study period.

Characteristic	Study sample				Baseline PED population (<i>n</i> = 2591) ^a
	Overall group <i>n</i> = 573	Discharged 444 (77)	Floor admit 92 (16)	PICU admit 38 (7)	
Age, median [IQR]	8.8 [6.8, 11.5]	8.8 [7, 11.5]	9 [6.3, 11.6]	8.2 [6, 10.7]	8.8 [6.8, 11.4]
Male	343 (60)	262 (59)	54 (59)	27 (71)	1581 (61)
Race					
African-American	325 (57)	261 (59)	43 (47)	21 (55)	1474 (57)
White	246 (43)	183 (41)	48 (52)	15 (39)	707 (40)
Other	3 (<1)	0	1 (1)	2 (6)	73 (3)
Hispanic ethnicity ^b	41 (7)	34 (8)	4 (4)	3 (8)	109 (6.4)
Medicaid	336 (59)	268 (60)	48 (52)	20 (63)	1524 (59)
Asthma control ^c	98 (17)	75 (17)	17 (18)	6 (16)	
Using iCCS	249 (43)	185 (42)	47 (51)	17 (45)	
SHS	226 (39)	169 (38)	31 (34)	23 (68)	
Prior PICU ^d	107 (19)	73 (16)	22 (24)	12 (32)	NA ^e
Prior ETI ^d	24 (4)	17 (4)	6 (7)	1 (3)	
Accessory muscle use	301 (52)	203 (46)	65 (71)	33 (87)	

Note: *n* (%) unless otherwise specified. iCCS = inhaled corticosteroid; SHS = second-hand smoke exposure.

^aBaseline population: all patients aged 5–17 years presenting to pediatric emergency department during study period with final primary diagnosis of asthma exacerbation by ICD code 493, including study sample.

^bHispanic ethnicity is not mutually exclusive of race and is included in the white racial category (25).

^cGlobal Initiative for Asthma chronic control criteria for preceding 3 months.

^dPrior PICU admission or endotracheal intubation for acute asthma.

^eNot available in database used to identify PED asthma population.

and the presenting PAS score was 5 [2, 9]. Accessory muscle use was noted in 301 (52%) participants. A greater proportion of participants aged 5–7 years (7.6%) had severe exacerbations than those aged 8–12 years (4.6%) or 13–17 years (0.9%) ($p = .03$, χ^2). There were 130 (24%) participants admitted to hospital, with 38 (7%) admitted to the PICU. Reasons for hospitalization included inadequate ventilation in 103 (79%), hypoxia in 49 (38%), and social circumstances or need for asthma education in 85 (65%).

Test performance rates and values for the entire cohort are presented in Table 3. Overall, 331 (58%) participants performed spirometry meeting full ATS/ERS criteria (univariate analyses), and an additional 36 (6%) performed high-quality spirometry. Participants aged 8–12 (67%) years were more likely to perform spirometry than those aged 5–7 years (48%) or those aged 13–17 years (58%) ($p < .001$, χ^2). The proportion of participants with severe exacerbations (PAS 12–15) able to perform spirometry (17%) was less

TABLE 3.—Performance success and overall values of tests of lung function and inflammation attempted by 573 unique participants aged 5–17 years with acute asthma exacerbations.

Test performance by age or severity ^a	FEV ₁ ^b	<i>p</i> ^c	Rint ^d	<i>p</i> ^c	eNO ^e	<i>p</i> ^c
Age (years)		<.001		.436		<.001
5–7	107 (48)		221 (98)		88 (45)	
8–12	161 (67)		232 (97)		174 (83)	
13–17	63 (58)		108 (99)		92 (93)	
Acute severity ^f		<.001		<.001		<.001
Normal	144 (60)		240 (100)		173 (84)	
Mild	82 (59)		135 (98)		80 (68)	
Moderate	100 (60)		161 (97)		93 (60)	
Severe	5 (17)		25 (86)		7 (29)	
Test values for entire cohort, median [IQR]	52 (37, 74)		187% (147, 244)		13 (8, 18)	
			0.79 kPa/l/s [0.56, 1.02]			

^aValues are *n* (%) of participants who attempted and were able to perform lung function test, unless otherwise specified.

^b% predicted FEV₁ by spirometry meeting all ATS criteria.

^c χ^2 (Pearson test).

^dAirway resistance by the interrupter technique. For ages 5–10 year, % predicted values are reported; for ages >10 years, absolute values (kPa/l/s) are reported.

^eeNO, exhaled nitric oxide, parts per billion. This test was not available for the first 68 participants.

^fPediatric Asthma Score: normal = 0–4; mild = 5–7; moderate = 8–11; severe = 12–15.

than the proportion with non-severe exacerbations (60%) ($p < .001$, χ^2). In a multivariable logistic regression model, age remained associated with performance of ATS/ERS criteria spirometry ($p < .0001$), whereas gender ($p = .6$), race ($p = .78$), and PAS severity as a continuous variable ($p = .06$) were not. Participants aged 8–12 years were more likely to perform spirometry than those aged 5–7 years (48%) (OR = 2.23, 95% CI: 1.45–3.11) or 13–17 years (58%) (OR = 1.61, 95% CI: 1.00–2.59). The nonlinear association of age with ability to perform full ATS/ERS criteria spirometry after adjustment for gender, race, and baseline acute asthma severity is depicted in Figure 2.

Almost all participants with mild and moderate exacerbations and 86% of those with severe exacerbations could perform Rint testing (Table 3). No multivariable analyses were performed as 98% of participants could perform Rint testing. FE_{NO} testing was performed by 354 (70%) out of 505 participants who attempted the test and by the majority of participants with mild and moderate exacerbations. However, only 45% of participants in the 5- to 7-year age group and 29% with severe exacerbations could perform this test ($p < .001$, χ^2). In a multivariable logistic regression model, performance of FE_{NO} testing was associated with age ($p < .0001$) and acute asthma severity ($p = .0001$), but not with gender or race. The nonlinear association of age with the ability to perform FE_{NO} in this model is depicted in Figure 2.

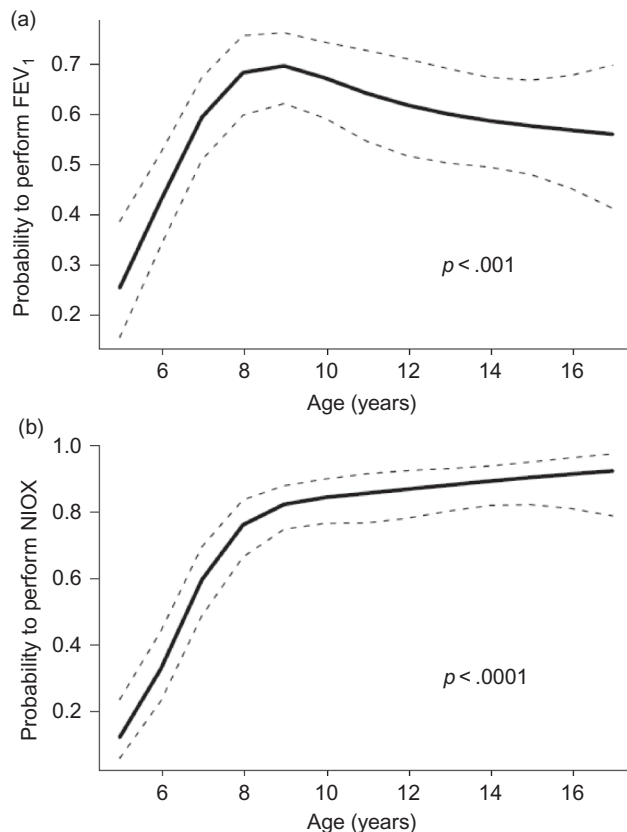


FIGURE 2.—Predicted probability to perform ATS criteria spirometry (a) and exhaled nitric oxide (b) with age adjusted for gender, race, and acute asthma severity using multivariable logistic regression models.

DISCUSSION

Many participants in this study were able to adequately perform noninvasive and objective tests of lung function and inflammation. However, there were differences in performance rates according to type of test, age group, and acute asthma severity. The values obtained for Rint and %FEV₁ in this cohort indicate significant lung function impairment. However, the median FE_{NO} value was normal, indicating that exacerbations in our cohort may not have resulted from eosinophilic airway inflammation (31, 32).

Although spirometry requires patient cooperation and coordination, tests meeting all ATS/ERS quality criteria were successfully performed by 58% of participants overall, with an additional 6% providing high-quality tests. Although few participants with severe exacerbations could perform spirometry testing (17%), the 60% participants with moderate episodes able to provide full ATS/ERS criteria studies are comparable to a prior study of peak expiratory flow measurement in a PED (33). %FEV₁ is the widely recognized criterion measure of asthma severity and, in contrast to peak flow measurement, the quality and variability of the FVC maneuvers are assessed. Attempts to perform this test may be warranted in the pediatric patient with an acute asthma exacerbation.

An unexpected finding was the greater proportion of participants aged 8–12 years (67%) who performed full ATS/ERS criteria spirometry than did participants aged 13–17 years (58%) when adjusted for acute asthma severity, gender, and race. This finding is consistent with investigations of child and adolescent willingness to participate in hypothetical, minimal-risk protocols, and with adolescents' concerns over the "hassle" of participation (30, 34). This is a worthwhile area for quality improvement. Additionally, in multivariable analysis, there was a non-significant trend toward an association of acute asthma severity with the ability to perform spirometry ($p = .06$) that was driven by those with the greatest severity.

Rint testing was performed successfully by almost all participants regardless of age or acute asthma severity. An alternative method for Rint measurement, impulse oscillometry, also requires only tidal breathing and passive patient cooperation and has been demonstrated to provide a valid and reproducible measure of lung function during exacerbations (35–37). Our study results indicate the clinical practicality of tidal breathing methods of lung function testing during acute asthma exacerbations.

Seventy percent of participants were able to perform FE_{NO} testing, a proportion nearly identical to that noted by Kwok and colleagues (11). Because this test requires a 6-sec, coordinated expiratory maneuver, we anticipate that a greater proportion can perform this measure once an acute asthma exacerbation is at least partially controlled. The utility of FE_{NO} for acute asthma management in the ED environment is still unclear (11).

The test values we observed in our cohort indicate clinically important decreases in lung function as

determined by %FEV₁ and Rint but essentially normal values for FE_{NO}. We believe that further study of Rint and FE_{NO} is warranted before they can be recommended for routine evaluation of acute asthma exacerbations in pediatric patients. In particular, further studies are needed of the validity of Rint and of normative values for patients above 10 years of age.

Our study has limitations. First, spectrum bias may be present because we used a convenience sample and did not recruit participants after 10 pm. Spirometry, in particular, requires coordination and is effort dependent on the part of the participant, and we have found it difficult to obtain these studies late at night. In addition, we had sufficient time and resources with which to assist participants in performing these measurements, and clinicians may not have similar results in other settings. Finally, the order of testing (Rint, FE_{NO}, and spirometry) may have affected the performance rates for FE_{NO} and spirometry, although Rint testing requires minimal effort.

Although our sample may not be representative of patients managed in other acute care settings, the demographic characteristics of our sample are comparable to the population of patients admitted to our PED with asthma exacerbations and include a broad spectrum of acute severity. In addition, our tertiary children's hospital PED manages most pediatric patients with acute asthma in urban, suburban, and rural regions. The full clinical variability of acute asthma can be difficult to precisely capture, yet we believe that our cohort represents a wide spectrum of both patient demographics and asthma presentations.

CONCLUSIONS

In conclusion, many pediatric patients with acute asthma exacerbations are able to perform noninvasive measures of lung function and inflammation. However, spirometry can only be obtained in approximately 60% of those with moderate and 17% of those with severe episodes, even under optimal circumstances in which a trained investigator has sufficient time to administer the study. In this study population, the measure of lung function might meaningfully inform clinical decision making, yet spirometry has limited applicability and thus might not be the most appropriate measure of lung function during acute exacerbations.

Alternatively, measures of Rint that require only tidal breathing are more widely applicable and warrant further investigation in this population. These noninvasive and objective measures of lung function might improve assessment and management of acute asthma exacerbations by accounting for variability of clinical exacerbation expression, decreasing provider variability, and facilitating individual patient management. Future investigations are warranted to examine the change of these lung function measurements during treatment and whether such change is predictive of the need for hospitalization and other management decisions.

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DECLARATION OF INTEREST

Aerocrine Corporation supplied the NIOX MINO nitric oxide monitor for this study. The authors have no other conflicts of interest to report. The authors alone are responsible for the content and writing of the paper.

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