



Figure 1. Magnetic resonance imaging of patient 2. Signs of diffuse hypoxic ischemia. Fluid-attenuated inversion recovery sequence: high-signal intensity (damaged tissue) in basal ganglia (caudate nucleus, striatum) (arrow A) and occipital lobe (visual cortex) (arrow B).

avoid the hypoxic brain damage. At the time of the described attacks, the diagnosis of HAE-C1-INH was unknown in patient 1 and known in patient 2.

Laryngeal attacks represent only approximately 1% of attacks in patients with HAE-C1-INH. The course of laryngeal attacks may include a predyspnea phase, a dyspnea phase, and a loss-of-consciousness phase.⁴ Complete recovery and death by asphyxiation have been reported in treated and untreated patients with HAE-C1-INH. Complete recovery without any residual impairment was reported for 324 untreated laryngeal attacks in 24 patients.⁵ Furthermore, complete recovery was reported in numerous laryngeal attacks of many patients treated on demand with various drugs.^{5–7} Death by asphyxiation in untreated, delayed treated, or inadequately treated patients has been reported many times and in numerous patients. One case was already mentioned in one of the earliest descriptions of HAE.⁸

We report a third kind of outcome, survivors of far advanced laryngeal attacks having irreversible disabilities as sequelae of brain damage after cardiac arrest and hypoxemia. Until now there have been no reports of patients with HAE-C1-INH who have survived a severe laryngeal attack that required reanimation measures and who subsequently remained permanently disabled because of hypoxic brain damage. The short course of the laryngeal attacks in the patients described here underlines the necessity of an early

diagnosis, a disease documentation, and an optimal treatment plan for laryngeal attacks in patients with HAE-C1-INH, including treatment with drugs that can rapidly counter the laryngeal attack.^{9,10}

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High exhaled nitric oxide levels correlate with nonadherence in acute asthmatic children



Nonadherence to asthma controller medication is associated with an increased number of acute exacerbations, increased

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asthma-related emergency department visits and childhood hospitalizations, and high health care costs.¹ The average medication adherence rate in children with asthma tends to be poor (<50%). Improving patient adherence is essential to achieving optimal outcomes.²

Measurement of fractional exhaled nitric oxide (FeNO) has been suggested as a sensitive, noninvasive indicator for monitoring

Table 1

Frequencies of Responses for Each Item of the Hill-Bone Medication Adherence Scale Short Form in Patients Hospitalized for Asthma

Hill-Bone Medication Adherence Scale	Response categories (N = 102), %			
	None of the time (1 point)	Some of the time (2 points)	Most of the time (3 points)	All of the time (4 points)
How often do you forget to take your asthma controller?	42	52	6	0
How often do you decide not to take your asthma controller?	73	18	7	2
How often do you forget to refill your prescription?	89	8	3	0
How often do you run out of asthma controller?	92	7	1	0
How often do you skip your controller before you go to your physician?	85	10	5	0
How often do you miss taking your controller when you feel better?	68	22	7	3
How often do you miss taking your controller when you feel sick?	89	5	6	0
How often do you take someone else's asthma controller?	92	6	2	0
How often do you miss taking your controllers when you are careless?	70	26	4	1

T-helper cell type 2 (T_H2)-mediated airway inflammation in children with asthma.^{3,4} Nonadherence to daily use of inhaled corticosteroids (ICSs) has been implicated as a key contributor to acute asthma exacerbation.⁵ Using the FeNO measurement in clinical practice is beneficial to predict future exacerbations and can be used to identify poor adherence to anti-inflammatory therapy in patients with allergic asthma.⁶ Feedback of FeNO findings during an acute asthma exacerbation offers a chance of improving parental knowledge of ICS characteristics by health providers. However, the feasibility and usefulness of FeNO as a diagnostic tool for identifying nonadherence to ICS in children with acute asthma exacerbation has not been established.

Identifying nonadherent patients with asthma is difficult and electronic monitoring is the only reliable method to assess ICS adherence, but this is not routinely available in clinical practice.⁵ The Hill-Bone Medication Adherence Scale (HBMAS) is a well-validated instrument for determining adherence to hypertension medications.⁷ In this study, a modified short-form HBMAS for asthma control was administered to assess the behavioral domains of asthma control treatment, taking medication, and keeping appointments. The availability of short screening tools can increase awareness and identify barriers of adherence to asthma control medication.⁸

The characteristics of the 102 subjects are shown in the eMethods section and eTable 1. Their median Childhood Asthma Control Test scores⁴ were 19.0 (18.4–20.1) and 30% had a previous emergency department visit, including 22% with a history of hospitalization in the past year. For asthma control treatment, 68% were prescribed an ICS, 13% were prescribed an ICS and a long-acting β_2 -adrenergic agonist, and 80% were prescribed

leukotriene modifiers. The HBMAS was used to dichotomize the responses as “perfect adherence” (9 points) and “imperfect adherence” (>9 points; Table 1), and only 32 patients (31%) with asthma reported perfect adherence (eTable 1).

The FeNO levels were significantly increased in the group with moderate to severe persistent compared with the groups with intermittent and mild persistent asthma ($P < .05$; eFig 1). The 102 hospitalized children with acute asthma were categorized as having a normal FeNO (<20 ppb; $n = 39$), an intermediate FeNO (20–35 ppb; $n = 30$), and a high FeNO (>35 ppb; $n = 33$) based on the American Thoracic Society (ATS) FeNO guidelines (Table 2). Patients in the intermediate and high FeNO groups had significantly higher total asthma attack rates, more emergency department visits in the past year, and higher *Dermatophagoides pteronyssinus*-specific immunoglobulin E levels compared with the normal FeNO group ($P < .05$; Table 2).

Based on the responses to the 9 items of the short-form HBMAS, 69% of enrolled patients had less than perfect adherence (>9 points) to asthma control. Approximately 5% to 10% of subjects had high scores for each question (>3 points), indicating that some patients needed more reinforcement with asthma education (Table 1). The high FeNO (>35 ppb) group had less than perfect HBMAS scores compared with the normal and intermediate FeNO groups ($P < .01$; Table 2).

We examined the FeNO levels 1 month after hospital discharge for high ($n = 70$) vs normal ($n = 32$) HBMAS scores based on the time of enrollment. The FeNO levels were decreased after a course of steroid treatment compared with during acute exacerbation ($P < .01$; eFig 2A). The group with high HBMAS scores for asthma control had persistently high FeNO levels ($P < .05$; eFig 2A). The log

Table 2Characteristics of Asthma Severity in Different FeNO Groups^a

	Normal FeNO (<20 ppb)	Intermediate FeNO (20–35 ppb)	High FeNO (>35 ppb)
Subjects	39	30	33
C-ACT scores	23.0 (20.3–22.9)	19.5 (17.9–21.0)	17.0 (15.3–17.5) ^{b,c}
ICS (equivalent to daily fluticasone)	100.0 (41.4–74.3)	100.0 (53.2–108.1)	100.0 (95.2–211.0) ^{b,c}
Days hospitalized in past year	4.0 (3.5–3.9)	4.0 (3.4–3.9)	4.0 (3.9–4.7) ^{b,c}
Total asthma attacks	0.0 (0.0–0.3)	1.0 (0.8–1.5) ^b	1.0 (0.5–3.5) ^b
Previous ED visit	0.0 (0.0–0.3)	0.0 (0.2–0.7) ^b	0.0 (0.3–0.9) ^b
Previous hospitalization	0.0 (0.0–0.2)	0.0 (0.0–0.7)	0.0 (0.1–1.0) ^b
PEFR % predicted	64.0 (59.8–66.1)	61.5 (57.1–63.6)	55.0 (48.6–57.6) ^{b,c}
Total IgE (IU)	354.5 (384.2–905.2)	574.0 (545.5–1001.5)	954 (832.9–1582.7) ^{b,c}
Der p (IU/ml)	51.2 (34.3–61.8)	100.0 (62.6–94.1) ^b	100.0 (53.5–84.5) ^b
Eosinophils (n/μL, %)	0.8 (1.2–3.3)	3.1 (2.6–4.9)	5.0 (3.5–6.1) ^b
HBMASSF	9.0 (9.5–10.3)	10.0 (10.1–11.7)	13.0 (13.0–15.8) ^{b,c}

Abbreviations: C-ACT, Childhood Asthma Control Test; Der p, *Dermatophagoides pteronyssinus*; ED, emergency department; FeNO, fractional exhaled nitric oxide; HBMASSF, Hill-Bone Medication Adherence Scale Short Form; ICS, inhaled corticosteroid; IgE, immunoglobulin E; PEFR, peak expiratory flow.

^aData are presented as median (95% confidence interval).

^b $P < .05$ vs normal FeNO (<20 ppb) group.

^c $P < .05$ for high FeNO (>35 ppb) vs intermediate FeNO (20–35 ppb) group.

HBMAS scores for asthma control positively correlated with log FeNO (Pearson correlation $\rho = 0.641$; $P < .01$; eFig 2B).

Because FeNO is a surrogate marker of eosinophilic inflammation based on limited studies, it is logical to believe asthma exacerbation is correlated with airway inflammation.³ Currently, there is no appropriate cutoff point for FeNO that can help identify nonadherence to asthma control in an acute setting. The 2011 ATS FeNO guidelines suggest that an FeNO level higher than 35 ppb in children can be interpreted as a high degree of T_H2-driven inflammation and increased risk of worsening symptoms and exacerbations.³ This study showed that asthma severity measurements were higher in the high FeNO group (FeNO >35 ppb), suggesting that persistent airway inflammation correlates with FeNO levels in patients with acute asthma. According to the ATS guidelines, intermediate FeNO values of 25 to 35 ppb in children should be interpreted with caution and persistent allergen exposure can be associated with higher FeNO levels.³ This study showed that only the high FeNO group, but not the intermediate FeNO group, had less than perfect HBMAS scores compared with the normal FeNO group.

Several research studies have been conducted to find the best use for FeNO measurements in predicting compliance markers. McNicholl et al⁶ reported that using the FeNO suppression test could identify nonadherence to ICS therapy in patients with difficult asthma. Using the Medication Adherence Report Scale, Koster et al⁹ reported that increased FeNO levels in children prescribed an ICS were associated with poor adherence. They suggested that increased FeNO levels could be indicative of ongoing airway inflammation caused by inadequate ICS treatment with under-prescription and poor compliance or poor inhaler technique.^{5,9}

To reflect a real clinical situation, we enrolled patients with upper respiratory infection. Malka et al¹⁰ found that high FeNO levels in children with acute asthma were not associated respiratory viral infection isolated by polymerase chain reaction. Asthma severity or an exacerbation also can increase FeNO levels. However, more research needs to be done to determine how best to incorporate the FeNO measurement with biomarkers to evaluate acute severity in the setting of an acute exacerbation.

In conclusion, in children hospitalized with severe exacerbations, use of the FeNO can help identify nonadherence. As such, FeNO and the HBMAS might be quantifiable indicators in monitoring asthma control therapy and provide an educational opportunity for improving parental knowledge of asthma control characteristics.

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Supplementary Data

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eMethods

Subjects

For this prospective cross-sectional study, 102 children with physician-diagnosed asthma admitted to Changhua Christian Children Hospital (Taiwan) with acute exacerbation of asthma were enrolled in this study. Pediatric patients (5–12 years old) with acute exacerbation were managed routinely at the pediatric emergency department (ED) based on Global Initiative for Asthma guidelines.¹ All enrolled patients completed the fractional exhaled nitric oxide (FeNO) measurement and peak expiratory flow rate after administration of the first dose of nebulized albuterol at 0.15 mg/kg and before systemic corticosteroids at the ED. The ED physicians did not have any knowledge of the FeNO results and independently determined patients' dispositions according to a standard treatment algorithm. Each child was assessed for asthma severity using the Childhood Asthma Control Test (C-ACT), and the Hill-Bone Medication Adherence Scale (HBMAS) was completed by investigators blinded to the results of FeNO or peak expiratory flow rate measurements. Blood sampling for immunoglobulin E, *Dermaphagoides pteronyssinus*-specific immunoglobulin E, and peripheral eosinophil counts were performed for each child. Patients with a history of cystic fibrosis, pulmonary hypertension, systemic lupus erythematosus, liver cirrhosis, who used oral corticosteroid in the past week at home, or who had acute febrile lower respiratory tract infection were excluded.² The hospital's institutional review board (I160114) approved the study and the parents of the children provided written informed consent.

Childhood Asthma Control Test

Symptoms were measured using the C-ACT, a 7-item questionnaire for assessing asthma control with 4 questions answered by the child and 3 questions answered by the parents. Although the C-ACT was developed for children 4 to 11 years of age, it was used for all subjects to consistently evaluate asthma control.³

Measurement of FeNO

The FeNO was measured before the peak expiratory flow rate (Astech Co, Port Washington, New York) at the ED. The FeNO levels were obtained using the on-line technique according to American Thoracic Society guidelines and measured on a NIOX Mino device (Aerocrine AB, Solna, Sweden), which uses electrochemistry, and followed previously published FeNO measurement protocols in the ED.^{3–6}

Adherence Measurements

The HBMAS is a well-validated instrument for determining adherence to hypertensive medications.⁷ The administered short-form HBMAS is a modified questionnaire with 9 short questions for adherence to asthma control, including an inhaled corticosteroid, an inhaled corticosteroid plus a long-acting β_2 -adrenergic agonist, and leukotriene modifiers, during the previous 4 weeks (eTable 1). The questionnaire was completed by parents and non-adherence was defined as a score higher than 9. To find the relation

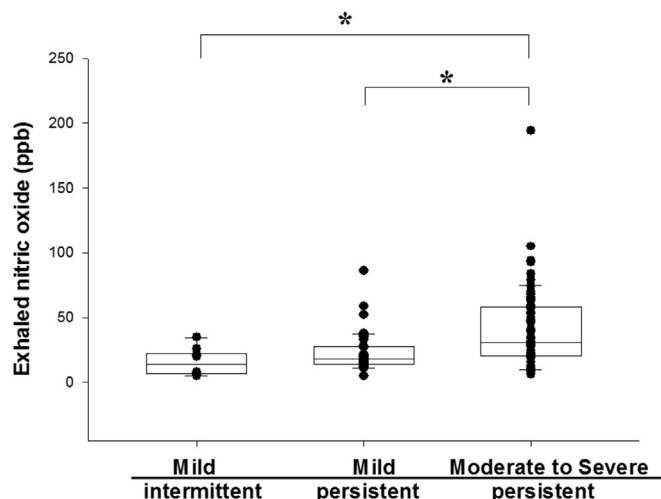


Figure 1. Mean fractional exhaled nitric oxide values in different Global Initiative for Asthma guideline-based asthma control groupings. * $P < .05$.

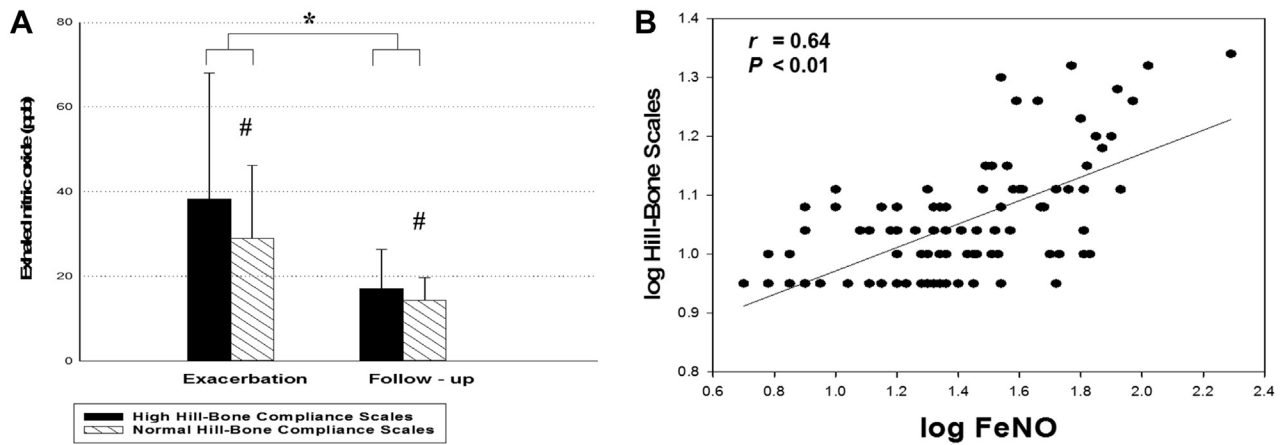
between FeNO and the HBMAS score for asthma control, we also examined FeNO levels 1 month after hospital discharge according to high vs normal HBMAS scores at the time of enrollment.

Statistical Analysis

All data are presented as median with 95% confidence interval. The differences of FeNO levels between acute exacerbation and 1 month after discharge were analyzed using Wilcoxon signed-rank test. Nonparametric tests (Kruskal-Wallis test followed by the Duncan test) were used to check for differences between groups. Correlations were analyzed by Spearman rank order correlation coefficient test. Significance was set at a P value less than .05.

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eFigure 2. (A) Fractional exhaled nitric oxide (FeNO) levels at acute exacerbation and 1 month after discharge for high ($n = 70$) vs normal ($n = 32$) Hill-Bone Medication Adherence Scale score for asthma control. $*P < .05$ after discharge; $\#P < .05$ vs normal Hill-Bone Medication Adherence Scale scores. (B) Graph of the relation between Hill-Bone Medication Adherence Scale score for asthma control vs FeNO in children with asthma. r , Spearman ρ correlation coefficient.

eTable 1

Subject Characteristics^a

Characteristic	Value
Patients	102
Mean age (y)	9.0 (8.8–9.9)
Boys/girls	56/46
GINA severity	
Intermittent	10 (10)
Mild persistent	35 (34)
Moderate persistent	51 (50)
Severe persistent	6 (6)
C-ACT scores	19.0 (18.4–20.1)
Previous ICU visit or intubations	3 (3)
ED visit in past year	31 (30)
Hospitalizations in past year	22 (22)
Home asthma medications	
Albuterol	102 (100)
ICS	70 (68)
Combined ICS + LABA	14 (13)
Leukotriene modifiers	82 (80)
PEFR % predicted	60.0 (57.2–61.4)
FeNO (ppb)	22.5 (26.7–37.3)
Total IgE (IU)	535.0 (688.6–1020.8)
Der p (IU/ml)	86.0 (57.6–73.8)
Eosinophils (n/μL, %)	2.3 (2.8–4.2)
HBMASF “perfect adherence” (9 points)	32 (31%)

Abbreviations: C-ACT, Childhood Asthma Control Test; Der p, *Dermatophagoides pteronyssinus*; ED, emergency department; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; HBMASF, Hill-Bone Medication Adherence Scale Short Form; ICS, inhaled corticosteroid; ICU, intensive care unit; IgE, immunoglobulin E; LABA, long-acting β_2 -adrenergic agonist; PEFR, peak expiratory flow.

^aData are presented as number (percentage) or median (95% confidence interval).