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Differentiating non-responders from responders in children with moderate and severe asthma exacerbations

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ABSTRACT

Objective: Our goal was to assess factors associated with non-response to treatment in children presenting to the Emergency Department (ED) with moderate and severe asthma exacerbations. **Methods:** A retrospective chart review was completed from 9/2014 to 2/2017 for patients with a discharge diagnosis of asthma exacerbation. The Modified Pulmonary Index Score (MPIS) was used to quantify illness acuity. The rate of change of MPIS per hour was calculated, and differentiated responders from non-responders. After examining a histogram of $\Delta\text{MPIS}/\text{h}$, a threshold of $\Delta\text{MPIS}/\text{h} > 0$ was used to define response for duration of ED stay. Children included were > 2 years and had initial MPIS > 10 . **Results:** Eight hundred and fifty-two children were included. There were 178 (21%) non-responders and 674 (79%) responders. Non-responders were significantly older (7.0 ± 4.0 versus 5.6 ± 3.2 years; $p < 0.001$), but there were no differences in gender, race, ethnicity or insurance status. There was also no statistical difference in time to first albuterol treatment (50 ± 41 versus 43 ± 40 min; $p = 0.05$), or in time to corticosteroid (95 ± 75 versus 79 ± 64 min; $p = 0.06$). Non-responders were significantly more likely to arrive by ambulance (OR 2.2; 95% CI 1.6–3.2), to be admitted to the hospital (OR 2.7; 95% CI 1.8–4.0), and to be admitted to the ICU (OR 5.0; 95% CI 3.1–8.1). **Conclusions:** One in five children with exacerbations did not respond to treatment. These children were older and more likely to be admitted. Non-measured factors, possibly genetic, may contribute to response to treatment.

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Introduction

Pediatric asthma is a common chronic disease affecting almost 9 million children in USA [1]. Exacerbations are common, and children frequently present to the Emergency Department (ED) [2]. In 2009, 679,000 children with asthma were seen in an ED [2]. Of these, 150,000 subsequently required hospital admission, and 10,000 children required admission to an Intensive Care Unit [3,4]. Determining which children will respond to therapy and which children will not respond to therapy is frequently challenging on initial presentation.

Evidenced-based guidelines and standardized scoring systems have been developed and many institutions have standardized protocols to treat asthma exacerbations in the ED [5–7]. However, there are no widely agreed upon asthma scoring systems in the ED that can clearly predict likelihood of hospitalization, need for higher level of care, or length of stay in the hospital if admitted [8]. Determining factors associated with a

patient's clinical course during an acute asthma exacerbation could improve appropriate resource utilization in our ED, including admitting specifically identified patients earlier in ED course which would open space for other patients to be evaluated more timely.

The Modified Pulmonary Index Score (MPIS) is a validated indicator of severity of illness in children with asthma and is reproducible across different types of health care providers (physicians, nurses and respiratory therapists) [9,10]. Our goal was to assess factors associated with non-response to treatment in children presenting to the ED with moderate and severe asthma exacerbations.

Methods

This study is a single-center retrospective chart review at a stand-alone urban pediatric hospital with approximately 65,000 annual ED visits. Inclusion criteria were patients with an ED diagnosis of asthma exacerbation

Table 1. The modified pulmonary index score.

Category	Score			
	0	1	2	3
Oxygen saturation, %	>95	93–95	90–92	<90
Accessory muscle use	None	Mild	Moderate	Severe
Inhalation–exhalation ratio	2:1	1:1	1:2	1:3
Wheezing	None	End expiratory	Inspiratory and expiratory wheeze, good aeration	Inspiratory and expiratory wheeze, decreased aeration
Heart rate, /min				
<3 years old	<120	120–140	141–160	>160
≥3 years old	<100	100–120	121–140	>140
Respiratory rate, /min				
<6 years old	≤30	31–45	46–60	>60
≥6 years old	≤20	21–35	36–50	>50

Six categories are evaluated: (1) oxygen saturation on room air, (2) accessory muscle use, (3) I:E ratio, (4) wheezing, (5) heart rate, and (6) respiratory rate. For each measurements or observations, a score (0–3) is assigned, resulting in a minimum score (0) and a maximum score (18).

during study period between April 2014 and February 2017 who had a MPIS score recorded during the ED visit and age ≥ 2 years. Exclusion criteria were patients transferred from outside the study ED, patients with no recorded MPIS values in their medical record for the ED visit, patients with primary diagnosis of bronchiolitis or pneumonia, and patients with chronic cardiac or lung disease other than asthma. This study was approved by the Institutional Review Board and informed consent was waived.

In the MPIS, six different categories are evaluated: (1) oxygen saturation on room air, (2) accessory muscle use, (3) inspiratory-to-expiratory flow ratio, (4) degree of wheezing, (5) heart rate, and (6) respiratory rate. For each of these six measurements or observations, a score of 0 to 3 is assigned, resulting in a minimum possible score of 0 and a maximum score of 18 [10] (Table 1).

The protocol at the study institution for managing asthma exacerbations in the ED instruct that all patients with history of ≥ 2 episodes of wheezing or diagnosis of asthma have an initial MPIS value recorded at triage. Children with $\text{MPIS} \leq 4$ are evaluated and monitored by a physician prior to discharge home. Those with an $\text{MPIS} \geq 5$ are placed on the treatment portion of the ED asthma pathway. The asthma pathway prescribes that patients with a previous diagnosis of asthma with $\text{MPIS} \geq 5$ are given a combined albuterol/ipratropium nebulizer treatment at triage. The pathway also instructs RN at triage to give oral steroids (dexamethasone 0.6 mg/kg up to 16 mg) by mouth at triage in those with $\text{MPIS} \geq 5$ with a known history of asthma. After initial treatment, patients are reassessed and given a new MPIS. Per pathway, patients with $\text{MPIS} \geq 7$ are started on an hour-long albuterol treatment, whereas MPIS 5–6 receive albuterol MDI with spacer and then discharged if improved after 30 min, and those ≤ 4 may be discharged home after initial treatment. These

children thereafter have an MPIS assessed at least hourly, and then just prior to discharge from the ED either to home or to hospital admission. The MPIS can be recorded and entered into the medical record by nurses, respiratory therapists, and resident or attending physicians.

Study patients were identified by searching the electronic medical records for all patients with a diagnosis of acute asthma exacerbation (by ICD-9 or ICD-10 code) during the study time frame. The following information was collected for each patient: age, sex, weight, zip code (proxy for geographic area), self-identified ethnicity, primary language, insurance type, emergency services index (ESI level 1–5) at triage, temperature, oxygen saturation, LOS in the ED, LOS in the hospital, disposition (admit, observation, discharge home from ED), service admitted to (critical care, pulmonary, inpatient medical team), chest X-ray obtained, return to ED within 72 h, readmission to hospital within 30 days, and medications received in the ED (albuterol, steroids).

The initial MPIS is defined as the first-recorded MPIS in the emergency department and the last MPIS is the last MPIS recorded in the emergency department prior to discharge or admission. The rate of change of MPIS per hour ($\Delta\text{MPIS}/\text{h}$) in the ED was calculated and used to differentiate responders from non-responders. The rate of change in MPIS/h [(last MPIS – initial MPIS)/h in ED] was calculated. Children were included if they were older than 2 years and had presented with a moderate or severe exacerbation (initial MPIS > 10).

Data were collected from the electronic medical record utilizing Qlikview Report. One hundred randomly selected charts were manually reviewed in the EMR to verify accuracy of data collected by Qlikview Report Analysis. No discrepancies were noted in the data during the review.

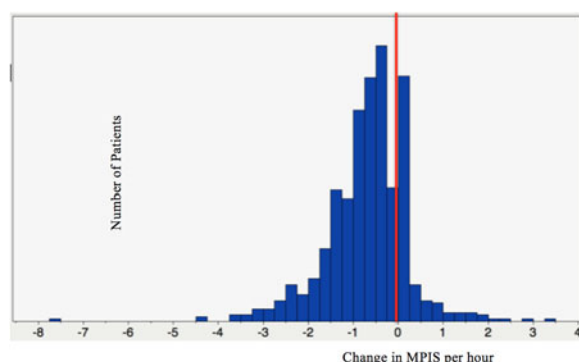


Figure 1. Histogram demonstrating change in MPIS per hour in study population.

Data were analyzed using JMP statistical software (version 10.0.1; SAS Institute Inc., Cary, NC) in collaboration with consultation from the Office of Research at the Connecticut Children's Medical Center. Data are reported as frequencies (%), as median with 25–75% interquartile range (IQR), or as mean $\pm$ standard deviation values, depending on the type and distribution of the variables. Children were categorized into “Responders” and “Non-Responders” and demographics and hospital data were compared using appropriate parametric tests and non-parametric statistics, including chi-square, *t*-tests, and Wilcoxon rank sum. A Shapiro–Wilk test was used to assess normality. A *p* values <0.05 was considered statistically significant.

Results

A total of 4943 patient encounters were analyzed for patients seen between April 2014 and February 2017, of which 872 were seen for acute asthma. Twenty patients with a diagnosis of acute asthma exacerbation could not be analyzed, as they did not have at least one MPIS score recorded in the medical record.

A total of 852 children were included in the analysis. An improvement in MPIS over time is associated with lower change in MPIS/h. After examining a histogram of Δ MPIS/h, there seemed to be two peaks in the distribution of the data, and a threshold of Δ MPIS/h > 0 was chosen as between these peaks and used to define response to therapy (Figure 1). In other words, those without an improvement in their MPIS score during the ED stay (regardless of length of ED stay) were defined as non-responders. Using this definition, there were 178 (21%) non-responders and 674 (79%) responders.

Comparisons between demographics and hospital course of non-responders and responders can be found in Table 2. Non-responders were significantly older (7.0 ± 4.0 versus 5.6 ± 3.2 years; $p < 0.001$), but

there were no differences in gender, race, ethnicity or insurance status. There was also no statistical difference in time to corticosteroid, but responders had a shorter time to their first albuterol treatment. Non-responders were significantly more likely to arrive by ambulance (OR 2.2; 95% CI 1.6–3.2) and less likely to have a chest X-ray in the ED than responders (OR 0.7; 95% CI 0.5–0.97). Non-responders were also significantly more likely to be admitted to the hospital (OR 2.7; 95% CI 1.8–4.0), and to be admitted to the ICU (OR 5.0; 95% CI 3.1–8.1). Very few of the children discharged from the hospital returned within 72 h and this did not differ by response.

Discussion

Despite similar asthma severity scores on admission, children who responded to therapy in the ED were younger, less likely to arrive by ambulance, more likely to get a chest X-ray, and received the first dose of albuterol more quickly than children who were non-responders. Non-responders were significantly more likely to be admitted to the hospital and to the ICU.

Even with implementation of evidenced-based standardized protocols, we are not always able to predict which patients may need to be admitted to the hospital upon arrival to the ED. This again highlights the complex nature of asthma management in the ED [11]. Response may also be related to asthma phenotype that may differ due to age of onset, triggering factors, and patterns of severity [12].

Responders in our study received albuterol sooner in their ED course. This demonstrates that earlier treatment intervention in the ED may improve patient care. It could also be speculated that responders are more albuterol naïve than non-responders.

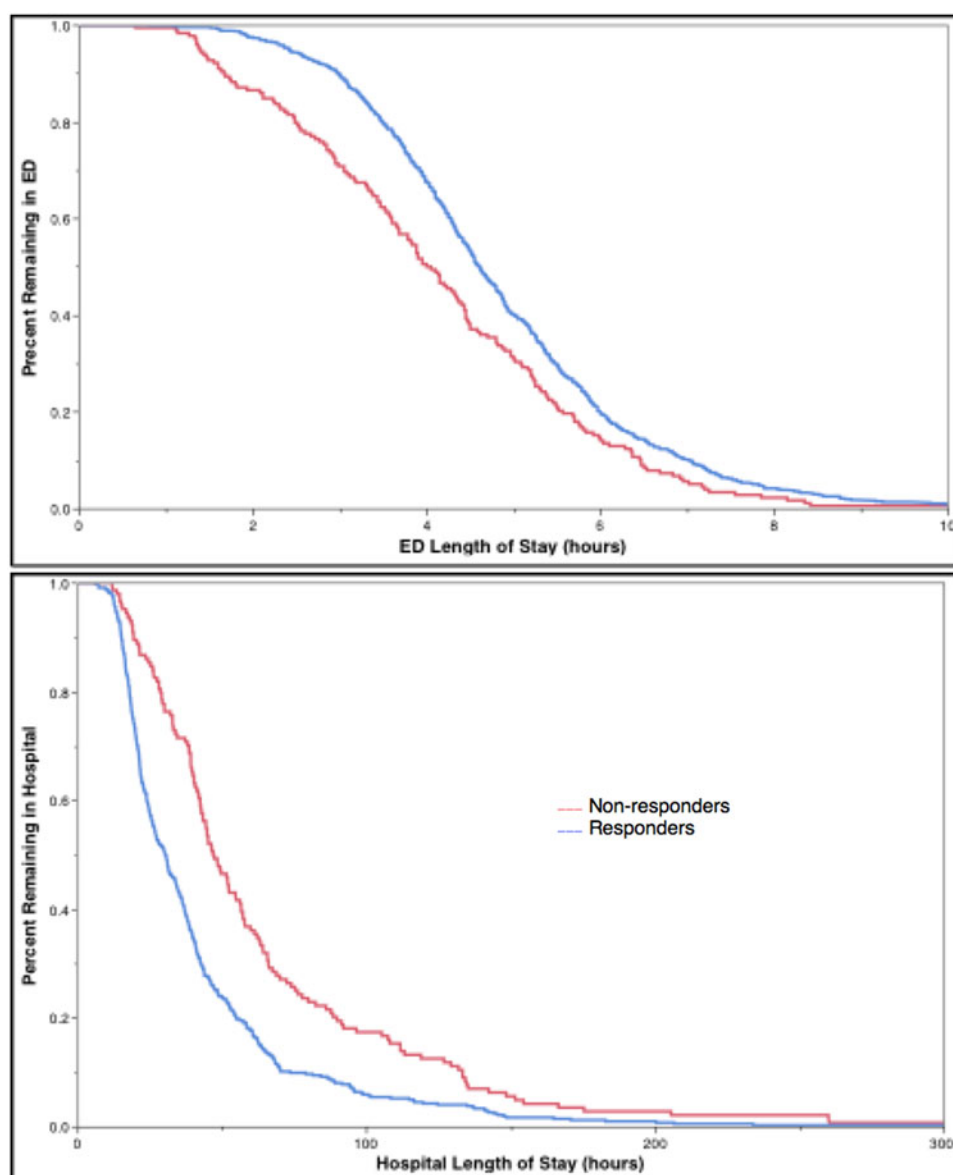
Interestingly, the initial MPIS was not associated with response, but rather it was the change in MPIS over time that predicted hospital admission. Providers frequently make judgments based on initial presentation; however, it may be that the change is more important to determining a patient's hospital course.

Responders had longer length of stays in the ED, but had shorter hospital length of stays in those admitted to the hospital. Responders were also less likely to be admitted to the hospital and to the ICU. It may be that rapid throughput in the ED caused the non-responders to have shorter ED length of stays. We speculate ED providers are more likely to determine disposition for admission sooner if patients are not improving, while those that patients with more improvement may be

Table 2. Demographics and outcomes of responders and non-responders.

	Non-responders	Responders	<i>p</i> value	OR (95% CI)
Age (years)	6.1 (3.7–9.2)	4.8 (3.3–6.8)	<0.001	
Male gender	52% (<i>n</i> = 92)	59% (<i>n</i> = 395)	0.10	1.3 (0.9–1.8)
Race				
Caucasian	30% (<i>n</i> = 54)	25% (<i>n</i> = 171)	0.18	0.8 (0.5–1.1)
African–American	29% (<i>n</i> = 52)	30% (<i>n</i> = 205)	0.78	1.1 (0.7–1.5)
Hispanic	62% (<i>n</i> = 110)	59% (<i>n</i> = 400)	0.43	0.9 (0.6–1.2)
Other	40% (<i>n</i> = 72)	44% (<i>n</i> = 298)	0.40	1.2 (0.8–1.6)
Public insurance	61% (<i>n</i> = 108)	64% (<i>n</i> = 434)	0.38	1.2 (0.8–1.6)
First pulse oximeter (%)	96 (94–99)	96 (94–98)	0.09	
ED LOS (h)	4.0 (2.8–5.3)	4.6 (3.7–5.8)	<0.001	
Hospital LOS (h)	46.9 (32.5–75.8)	39.3 (19.2–48.4)	<0.001	
Adm. to Hosp.	82% (<i>n</i> = 146)	63% (<i>n</i> = 425)	<0.001	2.7 (1.8–4.0)
Adm. to ICU	22% (<i>n</i> = 40)	5% (<i>n</i> = 37)	<0.001	5.0 (3.1–8.1)
CXR (Y/N)	51% (<i>n</i> = 91)	42% (<i>n</i> = 285)	0.04	0.7 (0.5–0.97)
Return to the ED within 72 h	2% (<i>n</i> = 13)	2% (<i>n</i> = 3)	1.00	1.1 (0.3–4.1)
Time to any steroid (min)	77 (34–133)	60 (34–105)	0.05	
Time to first albuterol (min)	35 (20–73)	28 (15–60)	0.01	
Initial MPIS	11 (10–13)	11 (10–12)	0.37	
Rate of improvement (MPIS/h)	0.32 ± 0.57	−0.98 ± 0.76	<0.001	
Arrived by ambulance (versus car)	39% (<i>n</i> = 68)	22% (<i>n</i> = 147)	<0.001	2.2 (1.6–3.2)

Data presented as median (25–75% IQR) or frequency (%).

**Figure 2.** Kaplan Meier Curves of ED and Hospital Length of Stay in Responders and Non-Responders.

given more observation time with hopes of improvement to discharge home from the ED.

This study is limited by several factors. First, this is a retrospective review done at an urban tertiary care Children's Hospital in the northeast region of USA. There may be other unmeasured clinical factors other than those measured/analyzed that are associated with the outcomes of interest. Additionally, since we only included children with an MPIS recorded, we may have missed some patients treated for asthma exacerbation in the emergency department if they did not have an MPIS recorded. However, it is our policy to obtain an MPIS on all children with acute asthma, so we do not believe we missed many children. Additionally our catchment area, which includes the greater Hartford area, has a significant asthma burden particularly in African American children and children of Puerto Rican ethnicity. Children of Puerto Rican ethnicity have been noted to have decreased response to albuterol therapy [13,14], and this population may have impacted our results.

Conclusions

In our single-center study, non-responders were more than 2.5 times more likely to be admitted to the hospital and five times more likely to be admitted to the ICU. This group may reflex an important phenotype for further study, and non-measured factors (possibly genetic) may have impacted response. Just as treatment approaches may be tailored to the individual in outpatient management, different approaches may be needed based age, triggers and pattern of severity. Additionally, standardized protocols can continue to guide physicians in management of patients with acute asthma in the ED but should focus on gaps in the system, improvements in delivering asthma medication and continuous quality improvement.

Disclosure statement

No potential conflict of interest was reported by the authors.

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