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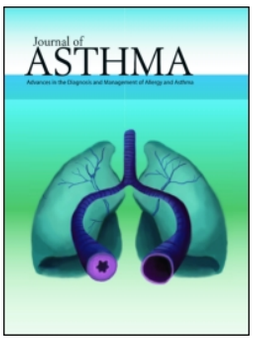

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Comparison of a rapid albuterol pathway with a standard pathway for the treatment of children with a moderate to severe asthma exacerbation in the emergency department

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ABSTRACT

Objective: The objective of this study was to determine if a rapid albuterol delivery pathway with a breath-enhanced nebulizer can reduce emergency department (ED) length of stay (LOS), while maintaining admission rates and side effects, when compared to a traditional asthma pathway with a standard jet nebulizer. *Methods*: Children aged 3–18 presenting to a large urban pediatric ED for asthma were enrolled if they were determined by pediatric asthma score to have a moderate to severe exacerbation. Subjects were randomized to either a standard treatment arm where they received up to 2 continuous albuterol nebulizations, or a rapid albuterol arm where they received up to 4 rapid albuterol treatments with a breath-enhanced nebulizer, depending on severity scoring. The primary endpoint was ED LOS from enrollment until disposition decision. Asthma scores, albuterol dose, side effects, and return visits were also recorded. *Results*: A total of 50 subjects were enrolled (25 in each arm). The study LOS was shorter in the rapid albuterol group (118 vs. 163 minutes, $p = 0.0002$). When total ED LOS was analyzed, the difference was no longer statistically significant (192 vs. 203 minutes, $p = 0.65$). There were no statistically significant differences with respect to admission rates, asthma score changes, side effects, or return visits. *Conclusion*: A rapid albuterol treatment pathway that utilizes a breath-enhanced nebulizer is an effective alternative to traditional pathways that utilize continuous nebulizations for children with moderate to severe asthma exacerbations in the ED.

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Background

Despite recent improvements in the long-term management of children with asthma, acute asthma exacerbations continue to be a leading cause for emergency department (ED) visits in children. According to the 2011 National Health Interview Survey (NHIS), conducted by the National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC), there are 25.9 million Americans, including 7.1 million children, living with a diagnosis of asthma [1,2]. In that same year, an estimated 4.1 million children (58%) had at least one asthma attack [1]. In 2010 there were 10.6 million physician office visits, 1.2 million hospital outpatient department visits, and 2.1 million emergency room visits due to asthma [1]. Health-care costs in the United States attributable to asthma are estimated to be approximately $56 billion annually, with children accounting for a significant proportion [1].

The mainstay of therapy for acute asthma exacerbations in the ED is rapid initiation of systemic glucocorticoids and inhaled short-acting beta-agonists (SABA) [3]. Short-term systemic glucocorticoids are generally regarded as safe and effective for acute asthma, and the dosing and route of administration have been standardized [3,4]. Dosing and routes of administration for inhaled SABA, however, have been more controversial. Studies evaluating dose ranges of 2.5–15 mg of albuterol per hour have yielded conflicting results concerning dose responsiveness, yet it is generally accepted that larger doses are required to yield similar improvements in lung function in sicker asthmatics [3,5–9]. There are many factors that affect the amount of drug delivered to the target structures (airway smooth muscle), including those related to the patient, device, and medication. Studies have shown that the amount of drug delivered to these areas can vary from as much as 20%

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in adults, to as little as 1% in some young children [10,11].

There is a great deal of controversy surrounding the ideal mode of delivery for inhaled SABA when treating acute asthma exacerbations in children. Despite literature suggesting that metered dose inhalers (MDI) with a spacer may be as effective as nebulizers for treating acute asthma in children, emergency providers in the United States and abroad have been reluctant to adopt this approach [12–17]. Many factors contributing to this reluctance have been identified, including physician and patient preference, respiratory therapist workload, concerns about technique reducing efficacy of the MDI, and the ability to deliver multiple medications at once with a nebulizer [13–17].

Nebulizer technology has advanced greatly over the last few decades. Newer devices are able to reliably aerosolize more of the medication in droplets with diameters in the respirable range [10,18,19]. Additionally, new classes of nebulizers have been developed to enhance delivery of medication to the target organ, reducing side effects and medication waste. The newer generation nebulizers include breath-actuated and breath-enhanced nebulizers. Breath-actuated nebulizers only nebulize medication during inspiration, enhancing delivery and reducing waste. The negative aspects of these nebulizers include their high cost, significantly longer nebulization times, and patients' difficulty with generating enough inspiratory pressure to activate the mechanism [18–20]. Breath-enhanced nebulizers will nebulize medication continuously, but a one-way valve limits medication release to the inspiratory phase. Patients receive a large bolus of medication early in the inspiratory phase, which is thought to enhance delivery. These devices have shorter run times when compared to the breath-actuated devices [10,18,19]. Several in vitro studies using lung simulators, and small clinical trials, have shown promising results regarding the enhanced delivery of medications with these next generation nebulizers [19,21–27]. Whether or not these results will translate to improved clinical outcomes is yet to be determined. In a recent clinical trial comparing a breath-actuated nebulizer to a standard nebulizer for the treatment of acute asthma in children, the authors concluded that the breath-actuated nebulizer led to reduced admission rates and a greater improvement in clinical asthma score, but did not reduce ED length of stay (LOS) (20).

To our knowledge, no study has compared a breath-enhanced nebulizer to a standard jet nebulizer for the treatment of acute asthma in children. The goal of this study was to determine if a rapid albuterol delivery pathway with a breath-enhanced nebulizer can reduce ED LOS, while maintaining admission rates, repeat visits, and side-effects, when compared to a traditional asthma pathway with a standard jet nebulizer. The Salter® Nebutech® HDN® (Salter Labs, Arvin, CA) was chosen because its breath-enhanced design and bolus delivery system may deliver greater amounts of albuterol to the small airways, in a shorter period of time, when compared with standard jet nebulizers and other nebulizers in its class.

Methods

The study site was a large, urban pediatric ED with approximately 80,000 visits per year. The study was approved by the hospital's Institutional Review Board. Children were eligible for enrollment if they were between 3 and 18 years of age and presented to the ED with an acute asthma exacerbation of at least moderate severity, defined by pediatric asthma score. The lower age cutoff was chosen because asthma diagnosis and beta agonist response can be unreliable in younger children. The upper age cutoff was chosen to include only pediatric subjects, as this is a pediatric asthma study. Children were required to have a history of physician-diagnosed asthma as reported by the parent or guardian. Children were enrolled when a research team member was available to obtain informed consent (convenience sample). Children were excluded from enrollment if the initial pediatric asthma score (PAS) was <3, immediate resuscitation was required, they had a history of chronic lung disease or congenital heart disease, they had any neuromuscular disease, intrathoracic foreign body was suspected, pregnancy or breast feeding, they received oral or parenteral steroids within the last week, or they had an allergy or other contraindication to one of the study medications.

Once consented, subjects were randomly assigned to one of two treatment arms, using a computerized randomization process. All subjects received 0.6 mg/kg oral dexamethasone (maximum 16 mg), as per the standard asthma pathway. For subjects unable to tolerate oral steroids, IV methylprednisolone could be substituted at a dose of 2 mg/kg (maximum 60 mg). All subjects had baseline vital signs (including heart rate, blood pressure, respiratory rate, and room air saturation), clinical asthma scores (PAS and PASS [28,29]), and peak expiratory flow rate (PEFR) recorded. The PAS is a validated clinical asthma score which is used commonly for severity scoring on pediatric ED asthma pathways, and is the score utilized in the current version of the study site's standard ED treatment algorithm [28].

Subjects randomized to the "standard" arm received treatments as dictated by the standard ED asthma pathway (Figure 1). All treatments were administered with the standard ED nebulizer, the Hudson RCI® Up-Draft® Neb-U-Mist® nebulizer (Teleflex Medical®, Research

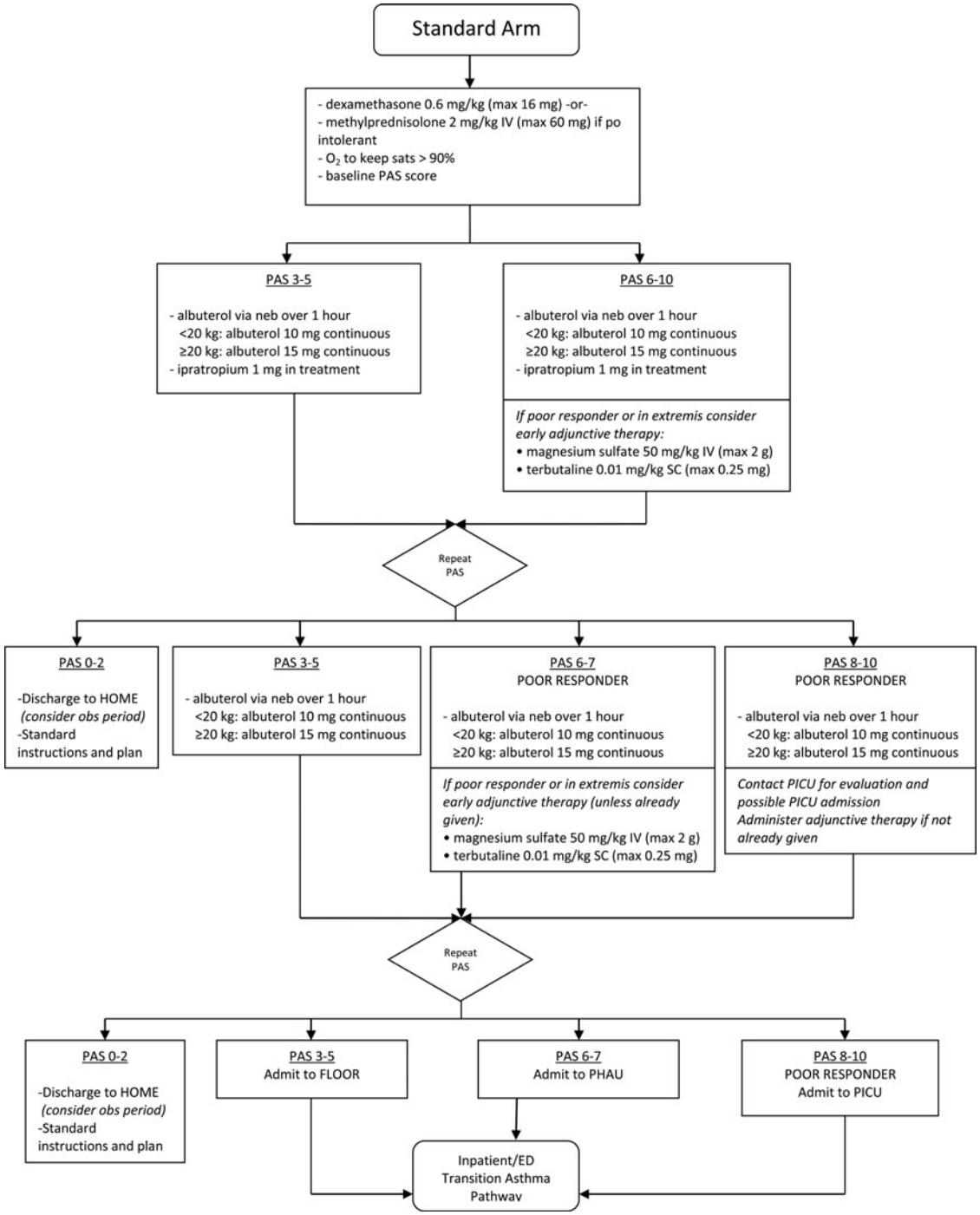

Figure 1. Standard pathway.

Triangle Park, NJ), and a simple mask (Hudson RCI®, Teleflex Medical®, Research Triangle Park, NJ). After the first hour of treatment, subjects in the standard arm received a repeat assessment, including all of the measurements collected at baseline as well as reported side effects. Subjects who scored PAS 0–2 were then discharged home, after an optional observation period, as per the pathway. Those who scored PAS >2 received a second treatment. At the end of the second treatment subjects were again reassessed, and measurements were obtained again. At that time, depending on the subject's PAS score, they were dispositioned to home, the floor, the pulmonary high acuity unit (PHAU), or the pediatric intensive care unit (PICU).

Subjects randomized to the "NebuTech®" arm received treatments as dictated by our trial pathway, referred to as the "rapid albuterol delivery pathway" (Figure 2). All nebulizations in this arm were administered via the NebuTech® HDN®, Breath-Enhanced High Density Jet Nebulizer (Salter Labs®, Arvin, CA). The respiratory therapist (RT) attempted to deliver all

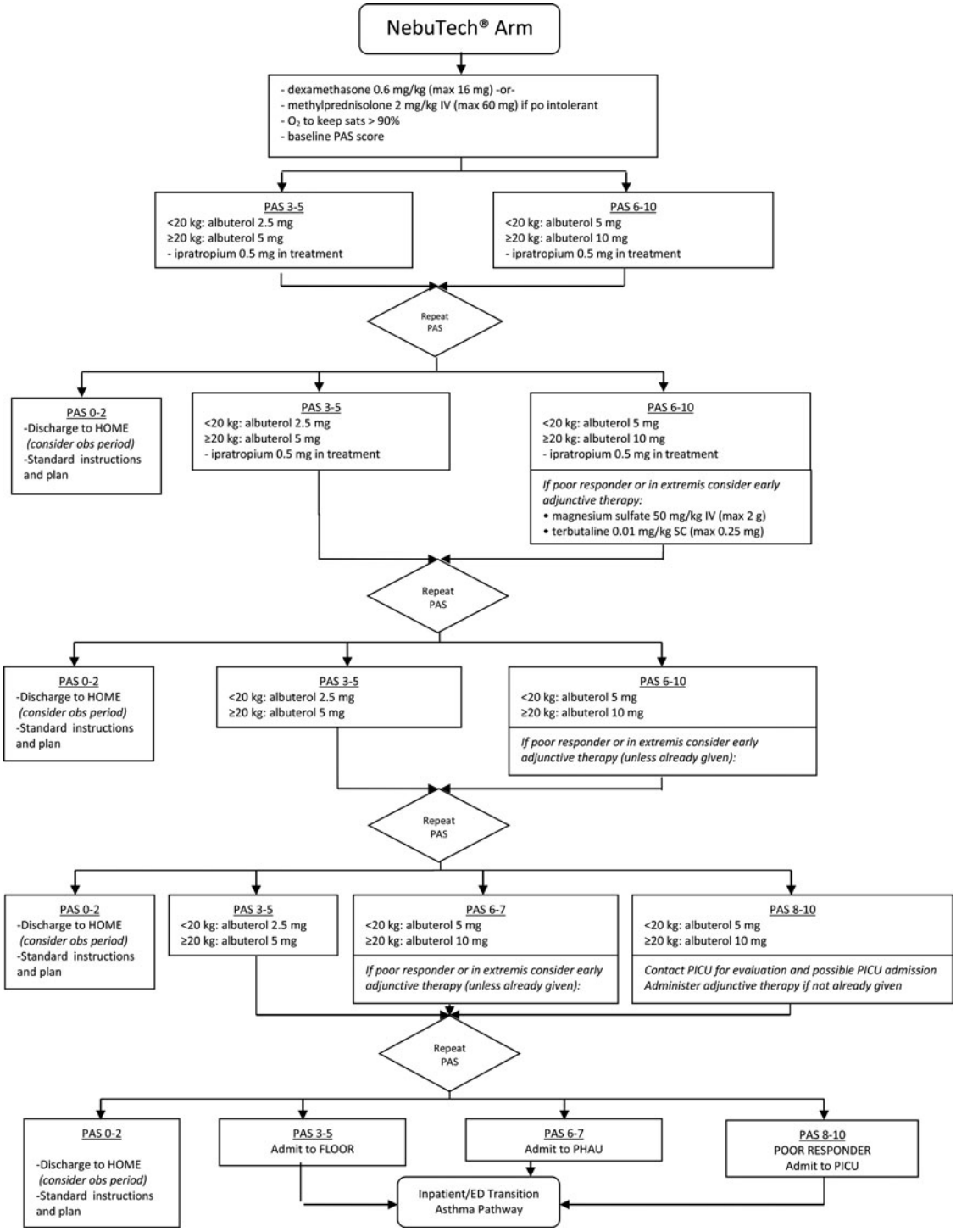

Figure 2. Rapid albuterol delivery pathway.

treatments with a mouthpiece, as that has been shown to be the most efficient and reliable mode of aerosol delivery for most children [30,31]. If the RT felt that the child could not effectively use a mouthpiece, a mask was used. The Nebutech® HDN® allows for a proprietary vented mask to be used, which still utilizes the breath-enhanced and bolus delivery features (I-Guard™ Valved Aerosol Delivery System, Salter Labs®, Arvin, CA). All treatments in the NebuTech® arm were given at a standard dilution of 5 ml (diluted with Normal Saline [NS] to a total volume of 5 ml as per the manufacturer's recommendation). Subjects in this arm received up to four treatments with parameters measured after each treatment, similar to the control arm. Subjects who completed four treatments were then dispositioned based on PAS score, similar to the control arm. Respiratory therapists

and attending physicians determining the final PAS score and ultimate disposition were not blinded to treatment allocation.

Following ED disposition, the treatment phase of the study concluded. All admitted subjects, from that point on, were treated using the standard inpatient asthma pathway and nebulizer. Admitted subjects were then followed throughout their hospital stay to determine hospital LOS, transfers to higher level of care, and adjuvant therapies utilized.

For the primary endpoint of ED LOS, the start point was the time of randomization. The endpoint was the time of disposition decision by the attending physician. These start and end points were chosen to minimize the impact of factors extraneous to the intervention being studied. Total ED LOS as measured by check-in time and ED departure time was also analyzed as a secondary outcome. All subjects who were discharged from the ED were contacted by a member of the research team about 72 hours after the ED visit. Any unscheduled ED visits, urgent care visits, primary care visits, or hospitalizations due to asthma were recorded. Prior studies have concluded that ED return visits for asthma greater than 72 hours from index visit discharge are unlikely to be related to care at the initial visit [32,33].

Statistical analysis

Descriptive statistics were used to characterize the samples. Continuous data are presented with means and standard deviations if normally distributed. Nonparametric and ordinal data are presented with medians and interquartile range. Categorical data are presented as percentages.

The primary endpoint (LOS) was normally distributed by the Shapiro–Wilk test, and was analyzed for significance using the student's *t*-test. Change in asthma score and total albuterol dose were analyzed using the nonparametric Wilcoxon Rank Sum test. Categorical data were analyzed with the Chi Square or Fisher's exact test as appropriate. Stepwise multivariable linear regression was then performed on the LOS outcomes to assess for confounding by the different baseline variables. Similarly, stepwise multivariable logistic regression was performed to assess for confounding of the hospital admission rates. A two-tailed level of 0.05 was used as the level of significance for all tests. Statistical analysis was performed using STATA 14 software (StataCorp LP, College Station, TX).

Sample size calculation

Initial sample size calculations were conducted using historical data for mean ED LOS and standard deviation for children with asthma. Using an effect size of 30 minutes with $\alpha = 0.05$ and power $= 0.8$, we estimated a sample size of 242 patients (121 per arm). There was a planned interim analysis after 50 patients in order to refine the sample size calculation given the potential for change in the mean and standard deviation for ED LOS after the implementation of a new standard-care asthma pathway. During this interim analysis it was determined that the primary endpoint already demonstrated a significant difference between the groups, so enrollment was halted.

Results

Between August 2013 and February 2015 a total of 50 subjects were enrolled (25 in each arm). The study was terminated for efficacy of the primary endpoint after the interim analysis. Baseline characteristics are displayed in Table 1. The groups were similar with the exception of differences in ethnicity, asthma severity, and baseline asthma score. The study LOS was shorter for the rapid albuterol arm (118 vs 163 minutes, $p = 0.0002$) (Table 2). When total ED LOS was analyzed, the resulting difference was no longer statistically significant (192 vs 203 minutes, $p = 0.65$) (Table 2). Stepwise multivariable linear regression was conducted to assess for the potential confounding effect of differences in baseline variables on the primary endpoint. The only variable that showed significance in the final model was the treatment arm

Table 1. Baseline Characteristics.

Baseline demographics Variable	Standard ($n = 25$)		Rapid/Nebutech® ($n = 25$)	
	Mean/ Median/%	SD/[IQR]	Mean/ Median/%	SD/[IQR]
Age (years)	6.9	[6.1–10.0]	6.8	[6.0–10.2]
Male	72%		64%	
Caucasian	16%		20%	
African American	44%		20%	
Hispanic	40%		56%	
Other	0%		4%	
Days of symptoms	2.0	[2–3.5]	2.0	[1–3]
Arrived EMS	4%		8%	
Albuterol doses past 24h	4.0	[2–5.5]	2.0	[0–4]
ICS prescribed	52%		60%	
ICS used	48%		44%	
LTI	20%		12%	
Mild intermittent	29%		45%	
Mild persistent	29%		13%	
Moderate persistent	16%		33%	
Severe persistent	25%		8%	
Baseline PAS	5.0	[4–7]	6.0	[4–6.5]
Baseline PASS	3.0	[2–4.5]	4.0	[2–4]
Baseline PF % predicted ($n = 27$)	37%	16%	39%	18%

Note. SD = standard deviation, IQR = interquartile range, ICS = inhaled corticosteroids, LTI = leukotriene inhibitor, PAS = pediatric asthma score, PASS = pediatric asthma severity score, PF = peak flow.

Table 2. Results.

	Standard ($n = 25$)		Rapid/Nebutech® ($n = 25$)		
Results	Mean/Median/%	SD/[IQR]	Mean/Median/%	SD/[IQR]	*p*-value
Study length of stay (minutes)	162.6	44.1	118.1	34.0	0.0002
Total length of stay (minutes)	202.8	83.2	192.1	79.2	0.65
Full pathway PAS Change ($n = 20$)	−4.0	[0 to −6]	−2.0	[−1 to −4]	0.54
Admitted (%)	36% (9)		44% (11)		0.56
Floor	32% (8)		40% (10)		0.56
IMC	0%		4% (1)		1.00
PICU	4% (1)		0%		1.00
Unscheduled return ($n = 35$)	11% (2)		0%		0.49
Total mg albuterol	15.0	[15–30]	15.0	[5–20]	0.08
Side effects (%)					
Nausea	12%		12%		1.00
Dizziness	4%		0%		1.00
Headache	4%		4%		1.00
Palpitations	8%		4%		1.00
Vomiting	4%		0%		1.00

Note. SD = standard deviation, IQR = interquartile range, PAS = pediatric asthma score, IMC = Intermediate Care, PICU = Pediatric Intensive Care Unit.

(coefficient = 54, $p = 0.005$, $R^2 = 0.27$). The admission rate was 44% for the rapid albuterol arm, and 36% for the standard arm ($p = 0.56$) (Table 2). These results also did not change when adjusted for baseline differences in the logistic regression model. The median albuterol dose was the same between the groups, and the rank sum test showed no significant difference ($p = 0.08$) (Table 2). There were two subjects in the control arm, and zero in the rapid albuterol arm that returned to the ED for asthma within 72 hours (Table 2). Both patients were admitted to the hospital. All observed adverse effects were minor and similar between the groups (Table 2).

Discussion

To our knowledge this is the first study comparing a rapid albuterol pathway utilizing a breath-enhanced nebulizer to a standard albuterol pathway for the treatment of acute asthma in children. Our results suggest that a rapid albuterol pathway is safe and effective, and can lead to reduced ED LOS. This information may be used to further refine asthma treatment algorithms in order to provide the most efficient care possible. Length of stay improvements in the ED setting are important because they translate to improved revenues for the hospital in the form of opportunity cost gains.

There are few clinical trials in children that utilize newer nebulizer technology for the treatment of acute asthma. In 2011, Sabato et al conducted a trial comparing the AeroEclipse breath-actuated nebulizer to a standard nebulizer for the treatment of acute asthma in children presenting to the ED [20]. The primary endpoint of that study was ED LOS, for which the authors were unable to demonstrate a significant difference. They offer a number of theories for the lack of difference, including many factors extraneous to the study, such as patient load, provider availability, and social issues. The authors did, however, show that the breath-actuated nebulizer yielded a greater improvement in asthma score and decreased admission rates relative to the standard nebulizer. There were several limitations to the study, including the inability for many of the children in the AeroEclipse arm to generate the inspiratory force to activate the mechanism, requiring the investigators to use the device in continuous nebulization mode [20].

Our study was able to demonstrate a reduction in ED LOS when disposition decision was used as the endpoint. When we looked at total LOS (arrival to departure), the difference was no longer significant. Similar to the Sabato study, we theorize that the reduction in the difference was likely due, at least in part, to factors outside of the control of the study, such as patient volume, social factors, and nurse availability for disposition. Also, due to prior asthma initiatives that encouraged physicians to observe albuterol responders for at least 2 hours in the ED before sending home, there may have been a tendency for providers to observe children longer if they rapidly achieved an asthma score that qualified for discharge on the pathway. This latter factor is difficult to decipher, but may be important when discussing the impact of measures aimed at providing a more rapid disposition for asthmatics in the ED.

It is important to note that this study did not measure the impact of the rapid albuterol arm on the respiratory therapists' workload. It is conceivable that widespread implementation of such a pathway would require increased staffing due to the need for more frequent assessment and treatment. These increased costs might partially offset the gains achieved by faster patient disposition.

There are several limitations to our study. Ideally we would have utilized a double blind or blinded assessor

design to remove the potential for bias on the part of the respiratory therapist or treating physician. This was not feasible given the drastically different run times of the two nebulizers and the design of the pathways. Additionally, the final sample size was too small to make any firm conclusions about our secondary endpoints, including admission rates, revisit rates, changes in asthma score, and total albuterol dose.

We interpret the results of this study as an encouraging first step in the design of more efficient ED asthma pathways. We feel that the principle of early and high-dose beta agonist delivery with the hope of rapidly assessing the degree of reversibility, in order to more efficiently disposition these patients is supported by this study. Future research should build on this principle by utilizing newer nebulizer technologies to more effectively deliver beta-agonists to the intended target, and minimize systemic absorption and side effects. Future studies may wish to utilize higher doses of albuterol in a rapid albuterol pathway given the positive results and favorable safety profile demonstrated in this study. The ultimate goal should be to develop a pathway that will rapidly and accurately differentiate asthmatics based on their degree of reversibility in order to maximize throughput and reduce opportunity costs in the ED.

Conclusion

A rapid albuterol treatment pathway that utilizes a breath-enhanced nebulizer is an effective alternative to traditional pathways that utilize continuous nebulizations for children with moderate to severe asthma exacerbations in the ED. Such a pathway may lead to decreases in LOS with resultant cost savings for the department.

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