Association between Timing of Albuterol and Care Escalation to the intensive care unit Among Pediatric Patients admitted with Status Asthmaticus

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Abstract
Children admitted to the ward for status asthmaticus may not receive the first albuterol treatment on schedule. We sought to determine if a difference in timing between scheduled and actual first dose of albuterol is associated with care escalation to the pediatric intensive care unit (PICU). We conducted a single-center case-control study of children 2-18 years admitted from the emergency department (ED) to the ward for status asthmaticus. Cases required transfer to the PICU within 24 hours of admission. Groups were compared using Fisher’s exact or Mann-Whitney U tests. Firth multivariable logistic regression estimated the association between dose timing and odds of transfer to the PICU. Groups did not differ by demographics, comorbidities, or asthma severity risk factors. The median (IQR) time difference between scheduled and administered first dose of albuterol was 0 (-14 to 63) minutes for cases and 16 (-6 to 42) minutes for controls (p=.4). Fifty percent of cases received delayed treatment compared to 63% of controls (p=.28). The adjusted analyses demonstrated that as the time difference between scheduled and administered albuterol increased by 1 minute, odds of care escalation to the PICU remained the same (OR=1.0, 95% CI: 0.9 to 1.0; p=.2). Receiving first albuterol treatment on the ward at a time different than scheduled was not associated with increased odds of transfer to PICU. Delayed albuterol administration did not vary with PICU transfer. Delays in treatment, when taken in the context of evidence-based asthma pathways, did not significantly impact hospital course or quality of care.

Introduction
Asthma is a chronic inflammatory respiratory disease that is widespread throughout the United States population with an increasing prevalence in children. According to the Centers for Disease Control and Prevention (CDC), total health care expenditure for pediatric asthma in 2019 was US $5.92 billion with inpatient and emergency department (ED) visits exerting the highest economic burden. Children admitted to the pediatric intensive care unit (PICU) for status asthmaticus accrue especially high medical charges. To provide better quality of care in asthma management, evidence-based clinical pathways are widely available and incorporate the use of inhaled β-adrenergic agonists along with systemic corticosteroids and other adjunctive therapies. Successful implementation of these pathways results in decreased length of hospital stay, reduced cost of hospitalization, and improved quality of care. However, clinicians and care teams may face challenges in adhering to these guidelines due to competing clinical demands.

Inpatient care pathways universally advocate for a regimented schedule of administering albuterol accompanied by repeated assessments for the ability to reduce the frequency of treatment. Selecting the initial frequency of albuterol administration is based on objective severity scoring systems such as Pediatric Asthma Severity Score (PASS). Such scoring systems are validated and used in various settings to accurately assess...
severity of disease and level of care, including frequency of albuterol administration. Adherence to a regimented albuterol frequency may theoretically improve asthma-related outcomes such as escalation of care. However, the impact of deviations from these frequencies on clinically relevant outcomes remains poorly described.

Among the small number of studies on this topic, a recent study showed PASS scores of at least 9 were associated with increased risk of transfer to the PICU within 24 hours of admission. However, this study did not evaluate the effect of delays in albuterol administration at the time of admission. If delays are shown to be associated with adverse outcomes, mechanisms to improve their timeliness could be implemented to ensure high quality and cost-effective care for children admitted with asthma. The objective of this study was therefore to determine if a difference in timing between scheduled and actual first dose of albuterol on the inpatient ward is associated with care escalation to the PICU within 24 hours of admission from the emergency department among pediatric patients admitted with status asthmaticus.

**Methods**

**Study Population, Setting, and Design**

This was a retrospective, matched case-control study using electronic medical record (EMR) data obtained from a single academic pediatric medical center in the southeastern United States. At our institution, asthma care is largely determined by a clinical practice guideline that provides recommendations for albuterol, corticosteroid, and other asthma adjunctive therapy for children presenting to the ED or hospitalized with asthma. Patients presenting with asthma are assessed by nurses, respiratory therapists, and/or clinicians and provided with a PASS score that helps to determine the interventions including albuterol frequency (every 1, 2, 3, or 4 hours), use of adjunctive therapies (e.g., magnesium sulfate, terbutaline), and disposition (home, general pediatric ward, or PICU). A PASS score of greater than 9 means likely admission to the hospital while a PASS score of 12 or above indicates likely admission to the PICU. If admitted to the ward, the PASS score determines initial albuterol frequency. It is also important to note that the institution at which the study was conducted only allows supplemental oxygen via nasal cannula or simple face mask on the ward and higher levels of respiratory support must be provided in the PICU.

Hospitalized patients aged 2-18 years admitted from the ED to the ward for status asthmaticus between May 2016 and August 2021 were included. The International Classification of Diseases, Tenth Revision diagnosis codes for reactive airway disease or asthma with accompanying status asthmaticus (J45.21, J45.22, J45.31, J45.32, J45.41, J45.42, J45.51, J45.52, J45.901, J45.902) were used to identify these patients. Patients who were directly admitted from referring institutions or who were not receiving scheduled short acting β-agonists for acute asthma management while admitted were excluded. Additionally, patients treated for acute pulmonary comorbidities (e.g., bronchiolitis, pneumonia), or those with airway anomalies or other chronic complex conditions were excluded. The study protocol was approved by our institutional review board.

**Study Variables and Definitions**

Clinical and demographic data were extracted from the patient’s EMR, including information about past medical history, asthma history, viral testing in the ED, asthma-specific therapies given during inpatient stay, and timing of therapies. The expected time of scheduled albuterol on the ward was determined by adding the number of hours from the initial assigned treatment frequency (i.e., 1 to 4 hours) to the time of the previously administered albuterol dose in the ED. Negative timing values indicated administration of albuterol ahead of schedule (i.e., ‘early’), whereas positive timing values indicated administration behind schedule (i.e., ‘late’).

**Case Identification**

Cases were defined as patients requiring transfer from the inpatient ward to the PICU within 24 hours of admission. This timeframe was chosen to reduce confounding from interventions or external factors that could potentially modify the illness course as hospitalization proceeded. Controls were defined as patients...
from the study population who did not require transfer from the inpatient ward to the PICU within 24 hours of admission. Cases were matched 1:4 to controls for age (months), sex (male vs female), and assigned albuterol frequency on admission (1 to 4 hours) using R’s MatchIt package.11

Statistical Analysis

Demographic and clinical data were described for cases and controls with summary statistics using percentages and frequencies for categorical variables and medians and interquartile ranges for continuous variables. Characteristics were compared across groups using Fisher’s exact test or Mann Whitney U tests where appropriate. Given that conditional logistic regression is a large-sample method12 we chose to fit unconditional multivariable Firth logistic regression models to estimate the association between dose timing and odds of transfer to the PICU. Firth logistic regression is a penalized likelihood-based method which provides bias reduction for small sample sizes and/or rare outcomes13,14 such as those observed in this study. Models were adjusted for an a priori determined group of covariates demonstrated to have an association with escalation of care, including any past PICU admission,15,16 PASS score ?9,10 any positive viral testing,17 any acute secondary diagnoses (besides respiratory),17 and other comorbidities (any).16,18 Additionally, we included age in months, sex, and albuterol frequency in the final model to adjust for potential residual confounding remaining after matching. Two-sided p-values < .05 were considered statistically significant. All analyses were conducted with Stata/SE Version 17.1 (StataCorp, LLC).

Results

Study Population

During the time period of interest, 594 patients were admitted to the general pediatric ward for status asthmaticus, 66 (11%) of whom were transferred to the PICU during their hospitalization. Forty-nine of these patients (74%) were transferred within the first 24 hours (Figure 1). After applying exclusion criteria, 22 patients and 88 matched controls were identified for comparison. The patients in the excluded subset (n=27) were treated for acute pulmonary comorbidities (e.g., bronchiolitis, pneumonia), and/or had airway anomalies or other chronic complex conditions. The baseline demographics, past medical history, and past asthma history of our study population are described in Table 1. Cases and controls did not differ significantly with respect to age, sex, race, ethnicity, or health insurance status. There were also no observed inter-group statistical differences in terms of chronic comorbidities, number of comorbidities, and BMI percentile during admission.

Asthma History

Cases were more likely to have a prior asthma diagnosis compared to controls (p =.02). There were no observed inter-group statistical differences with respect to National Heart Lung and Blood Institute (NHLBI) asthma severity classification, use of home asthma controller medications, or adherence based on documented history. Moreover, there were no observed differences between cases and controls with respect to having an established pulmonologist, exposure to pets at home, immediate family history of asthma, second-hand smoke exposure, or presence of housing instability.

Cases more frequently had a history of prior hospitalizations for asthma or bronchiolitis (p =.01) or a history of prior admissions to the PICU for asthma or bronchiolitis (p =.003). There were no observed differences between cases and controls with respect to number of ED visits in the preceding 12 months. However, more cases than controls had $\geq 1$ admission(s) to for asthma in the preceding 12 months (p =.002).

Emergency Department Course

Table 2 describes the ED and hospital course among cases and controls. The median initial PASS scores upon arrival to ED were similar between groups (Cases: 9 [IQR:7 to 12], controls: 10 [IQR:7 to 12]; p =.7). There were no differences with respect to positive viral testing, either at our facility or an outside facility prior to presentation, (p =.06) or with respect to presence of hypoxemia in the ED (p =.8). Cases and controls received similar medications in the ED with no inter-group differences among those receiving
albuterol/ipratropium nebulization, corticosteroids, magnesium, epinephrine, fluid bolus, or antibiotics. The median time from placement of the admission order by the ED healthcare provider to arrival of the patient on the hospital ward was 1.2 hours (IQR: 0.8 to 1.4) for cases and 1.0 hours (IQR: 0.8 to 1.2) for controls. There were differences in assigned albuterol frequency (every 1 to 4 hours) between groups at the time of admission.

Hospital Course

Once admitted to the hospital ward, a higher proportion of cases than controls required adjunctive treatment with magnesium ($p < .0001$) and albuterol/ipratropium ($p < .0001$). Cases remained on the hospital ward for a median of 7.4 (IQR 4.2 to 15.5) hours prior to transfer to the PICU. Once in the PICU, cases required additional adjunctive therapies with magnesium (31.8%) albuterol/ipratropium (22.7%), terbutaline (4.6%), and helium/oxygen (4.6%).

Groups differed significantly with respect to the highest level of respiratory support needed during their hospitalization, inclusive of time in the PICU ($p < .0001$). Among cases, 36.4% required nasal cannula, 36.4% required heated high flow nasal cannula, 9.1% required CPAP or BiPAP, 4.6% required intubation and mechanical ventilation, and 13.6% required no support. Among controls, 38.6% required nasal cannula and 61.4% required no support.

Cases had a significantly longer median length of stay compared to controls (Cases: 2.9 days [IQR 2.4 to 4.6 days], controls: 1.2 days [0.8 to 1.7 days]; $p < .0001$). Following discharge, there was no inter-group difference on return to the emergency department ($p = .4$) or readmission (cases: 0%, controls: 0%) for asthma within 30 days.

Deviations in Timing of Albuterol Administration and PICU Transfer

As seen in Figure 2, the median time difference between the scheduled and administered first dose of albuterol among cases was 0 minutes (IQR: -14 to 63, range -40 to 174) and 16 minutes (IQR: -6 to 42, range -115 to 184) among controls ($p = .4$), where positive times indicate administration delays and negative times indicate dosing ahead of schedule. Among 11 cases with delayed albuterol administration, the median time delay was 63 minutes (IQR 14 to 82, range 2 to 174). Among 55 controls with delayed albuterol administration, the median time delay time was 36 minutes (IQR 17 to 101, range 2 to 184; $p > .9$).

As seen in Figure 3, the time difference between scheduled and administered albuterol was not associated with increased odds of transfer to the PICU (adjusted OR: 1.0, 95% CI: 0.9 to 1.0) after covariate adjustment for past PICU admission, PASS score [$\geq 9$], any positive viral testing, any acute secondary diagnoses (other than respiratory), and other comorbidities (any). Adjustment for PASS score [$\geq 9$] was performed based on existing evidence that assigned values above this threshold are associated with escalation of inpatient services to the PICU within 24 hours of admission. However, past history of admission to the PICU due to asthma was associated with increased odds of transfer (adjusted OR: 4.3, 95% CI: 1.1 to 16.7). No other significant associations were observed.

Discussion

In this study of children hospitalized for status asthmaticus, deviations in the timing of the first dose of albuterol on the pediatric ward were not associated with increased odds of care escalation to the PICU. This is the first assessment of this relationship to our knowledge and offers insight about the importance of this first treatment in the broader context of healthcare utilization and cost during asthma admissions. There is substantial evidence to show that adherence to asthma pathways can improve quality of care, shorten overall length of stay, and reduce healthcare-related costs. However, while clinical pathways included repeated clinical assessments and regularly scheduled treatments throughout the course of hospitalization, there is a paucity of evidence describing whether deviations from prescribed frequencies of interventions results in adverse clinical outcomes. Our findings suggest that the timing of the first albuterol treatment upon arrival to the ward may not significantly impact hospital course or quality of care in the context of pathway implementation.
One possible explanation for this observation is the routine use of albuterol/ipratropium and systemic steroids in the ED while patients are undergoing initial evaluation for asthma exacerbation severity—a practice routinely incorporated into structured asthma pathways. There is ample evidence to demonstrate that early treatment in the ED can lead to improved outcomes for patients in status asthmaticus, including the ability to be discharged home from the ED.\textsuperscript{19,20,21} It is possible that early administration of steroids and albuterol/ipratropium in the ED sufficiently mitigates airway inflammation and bronchospasm and delayed symptom progression as children transition from the ED to the ward. Thus, early use of these medications in the ED may alleviate the need for strict adherence to timely administration of albuterol upon transition to the ward.

Broader implications of our findings may also include support of asthma pathways that involve alternative albuterol weaning strategies. Existing studies of the implementation of asthma pathways in hospital systems often involve weaning of albuterol in hourly increments from “continuous” to “every 4 hours”—an approach used at our center during the study period. Successful implementation of pathways using this hourly weaning protocol has been associated with significant reductions in overall length of stay, lower hospital resource utilization, and decreased hospital charges.\textsuperscript{22-26} However, these benefits may be due to the timely clinical re-assessments resulting from hourly weaning protocols as opposed to any realized physiologic or clinical benefit to the patient, the latter of which has not been thoroughly evaluated. In our center, the majority of cases (73\%) and controls (81\%) received treatment up to one hour after the scheduled administration time. Although we only evaluated the first albuterol treatment received on the ward, this finding may help support a strategy for safely weaning in larger increments (e.g., from “continuous” to “every 2 hours” to “every 4 hours”). However, further studies specifically evaluating longer versus shorter weaning increments are needed.

Previous admission to the PICU for status asthmaticus was associated with increased odds of PICU transfer. Significant intergroup differences were also observed based on historical factors including existing asthma diagnosis and past hospitalization for asthma. These historical risk factors are known to be associated with similar worsened asthma outcomes, including increased risk of future exacerbation necessitating admission to the hospital.\textsuperscript{15,18} Our findings suggest that children with a high-risk asthma history may also be prone to care escalation to the PICU once admitted to the general hospital ward. Once in the PICU, cases required more intensive therapies. They also had a longer overall length of stay compared to controls (median 2.9 vs 1.2 days). These findings indicate a need for individualized assessment of each child based on existing risk factors to better understand and manage disease progression in the hospital setting. Further investigation into why these risk factor are associated with care escalation could ultimately minimize health care cost and utilization for this highest risk group.

We acknowledge several limitations to this study. First, only the initial treatment with albuterol on the hospital ward was evaluated. Established asthma pathways call for repeated treatments and assessments and it is unknown if delays in subsequent or multiple treatments or if delays in treatments after the first 24 hours could contribute to care escalation. Second, our analysis may have been subject to residual confounding, as we could not adjust for all known asthma risk factors associated with increased need for intensive care, including a history of requiring mechanical ventilation, more severe chronic asthma, poorer control of asthma, and exposure to smoking (active or passive).\textsuperscript{10,16,17} Third, our study was limited by its retrospective design, which was necessary since our outcome of interest is relatively rare. As a result, our study design may have contained sampling bias due to incomplete or inaccurate documentation. Lastly, our results may not be generalizable to all pediatric hospitals since it was conducted in a single tertiary care center. Larger, multicenter studies would be needed to better understand the impact of albuterol treatment delays on a broader scale.

In conclusion, we found that deviations in the timing of the first dose of albuterol on the pediatric ward were not associated with increased odds of care escalation to the PICU. The rationale for this finding requires further investigation but may be due to a protective effect of early administration of steroids and bronchodilators in the ED or may be due to the fact that measured deviations in timing on the ward were
relatively short. Our data suggest that deviations in albuterol timing may not significantly impact clinical course when children are receiving care according to well-established, evidence-based, inpatient pediatric asthma pathways. However, we did identify several historical risk factors that were associated with care escalation. Further clarifying these risk factors and identifying areas of intervention to reduce the cost of hospitalization and improve the quality of care for high risk children admitted with status asthmaticus should be a priority for future studies.

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