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To cite this article: AdaT. Lin, Melissa Moore-Clingenpeel & Todd J. Karsies (2019): Comparison of Two Continuous Nebulized Albuterol Doses in Critically Ill Children with Status Asthmaticus, Journal of Asthma, DOI: [10.1080/02770903.2019.1623249](https://doi.org/10.1080/02770903.2019.1623249)

To link to this article: <https://doi.org/10.1080/02770903.2019.1623249>



Accepted author version posted online: 23 May 2019.



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Title: Comparison of Two Continuous Nebulized Albuterol Doses in Critically Ill Children with Status Asthmaticus

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Running Title: Low v. high dose albuterol for status asthmaticus

Key Words: wheezing, bronchial asthma, bronchodilator agents, intensive care units, pediatric

ABSTRACT

Objectives: Continuous nebulized albuterol is frequently used to treat children with status asthmaticus in the pediatric intensive care unit (PICU) but can have cardiovascular side effects. Limited data exist comparing different dosages. The purpose of this study was to compare hemodynamic side effects of two continuous albuterol doses (10 mg/hr vs 25 mg/hr). Our hypothesis was that lower-dose albuterol would be associated with lower toxicity without increased need for adjunctive therapies.

Methods: We conducted a retrospective cohort study of all children over 2 years old receiving continuous nebulized albuterol for status asthmaticus in our PICU from 2011-2013. Standard initial therapy was intravenous steroids and continuous nebulized albuterol. Patients receiving 10 mg/hr albuterol were compared to those receiving 25 mg/hr. Clinical outcomes, including the need for additional asthma therapies as well as hypotension requiring fluid resuscitation, were evaluated.

Results: 632 patients were studied (342 received 10 mg/hr, 290 received 25 mg/hr). Children in the lower-dose group received less fluid resuscitation without increased adjunctive therapies when adjusted for confounders. Those in the 25 mg/hr group receiving 17% higher bolus volume. Those receiving lower-dose albuterol had shorter adjusted PICU and hospital lengths of stay.

Conclusions: In our PICU cohort of children with status asthmaticus, use of 10 mg/hr continuous albuterol was associated with lower fluid bolus resuscitation without more

adjunctive therapies. These findings support the safety of lower doses in this population. Prospective studies evaluating the efficacy and toxicity of specific continuous albuterol dosages in critically ill children with status asthmaticus are warranted.

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INTRODUCTION

Status asthmaticus is a life threatening condition in children and one of the most common reasons for admission to the pediatric intensive care unit (PICU). Data suggest a plateau in asthma prevalence and decrease in hospital admissions for asthma; however, the rate of ICU care for children with status asthmaticus is on the rise (1, 2). While there are extensive evidence-based guidelines for the management of pediatric asthma, most of the data and recommendations focus on prevention, outpatient management, or routine inpatient management and exclude patients admitted to intensive care (3).

The most commonly used bronchodilator in critically ill children with status asthmaticus is inhaled albuterol in the continuous aerosolized form. A recent report found that approximately 90% of patients treated for status asthmaticus in United States PICUs received this therapy (4). Continuous albuterol is one of the few evidence-based therapies used in PICU asthma care (5). However, it is not without potentially significant side effects, with dose-dependent diastolic hypotension, tachycardia, and/or concern for myocardial injury being reported for the majority of those receiving continuous albuterol (6, 7).

Despite evidence for using continuous albuterol in children with status asthmaticus, specific evidence-based dosing regimens are lacking. In 2007 the National Heart, Lung, and Blood Institute (NHLBI) recommended that pediatric patients with exacerbations be started on albuterol at either a 0.15-0.30 mg/kg dose every 1-4 hours or a dosage of up to 0.5 mg/kg/hr (10-15 mg/hr for adults) of continuous albuterol (3). Evidence since

then, however, suggests that in practice doses still exceed recommended levels 60% of the time for moderate exacerbations and every time for severe exacerbations (8). Moreover, dosing for continuous albuterol has been reported as high as 75mg/hr and 150 mg/hr for moderate and severe exacerbations, respectively (9). No prospective studies have examined dose-dependent efficacy for continuous albuterol in the PICU, and recent studies discussing continuous albuterol dosing are based on individual opinion or local consensus (10, 11). Due to local clinician concerns about toxicity (primarily hypotension and tachycardia), our local dosing options were reduced from higher doses to 10 mg/hr and 25 mg/hr in 2011.

Given the lack of evidence regarding dosing, coupled with the dosing transition that was occurring in our ICU, we designed a retrospective study to compare toxicity and need for adjunctive therapies in critically ill children requiring continuous albuterol for status asthmaticus using these doses. Our hypothesis was that lower dose continuous albuterol (10 mg/hr) would be associated with lower cardiovascular toxicity (as evidenced by a need for fewer fluid boluses) without resulting in increased need for adjunctive therapies, compared to 25 mg/hr.

METHODS

We conducted a retrospective study in a single quaternary care PICU using an automated data collection program, Qlikview (Qliktech International AB, Radnor, PA) using data from our enterprise data warehouse. We identified study patients utilizing the following search parameters: ages two years and older, continuous albuterol with a

dose of either 10 mg/hr or albuterol 25 mg/hr, and discharge date between January 1, 2011 and December 31, 2013. Patients receiving both continuous albuterol dosages were excluded. Children younger than age two were excluded in order to avoid potential bronchiolitis-related bronchospasm. To ensure statistical independence, repeat visits by the same patient were excluded (75 encounters). Clinical data were confirmed by medical records review.

The following therapies were defined as adjuncts: non-invasive ventilation (NIV), invasive mechanical ventilation, heliox, terbutaline, magnesium, aminophylline, ketamine, and extracorporeal membrane oxygenation. In addition, the asthma clinical score (ACS) at time of admission to the PICU was recorded using a locally-adapted version of the Modified Pulmonary Index Score (12) (see online supplement Figure S1). Fluid resuscitation, both number and total volume of fluid boluses, was also evaluated. PICU length of stay (LOS) was calculated from the time of PICU admission until the time of PICU discharge, and hospital length of stay (LOS) was calculated from the time of hospital admission until the time of hospital discharge.

In our institution, all patients receiving continuous bronchodilator therapies or acute mechanical ventilation are admitted to the ICU. Local PICU asthma management was at the discretion of the attending intensivist although there were treatment guidelines that were typically followed for escalation and de-escalation of therapy (see online supplement Figure S2). The tiers of therapies in the treatment guideline were based on evidence for specific therapies as well as the potential side effects and invasiveness of

the therapies. All PICU patients are initially treated with continuous albuterol, systemic steroids, and aerosolized ipratropium. If respiratory distress and wheezing persist despite these therapies, adjunctive therapies are initiated based on local treatment guidelines. Fixed dosing rather than weight-based dosing of continuous albuterol was used throughout the study period. Fluid resuscitation was also at the discretion of the intensivist, both in terms of timing and amount, but was typically given for treatment of hypotension. All patients received maintenance intravenous fluids while on ICU therapies.

This study was approved by the local Institutional Review Board with a waiver of informed consent.

Statistical Analysis:

We report standard descriptive statistics to summarize patient characteristics and used chi-square/Fisher's exact tests and Wilcoxon-Mann-Whitney tests, as appropriate, to compare characteristics between the two albuterol dosage groups. Assumption of normality was evaluated using quantile-quantile plots and Shapiro-Wilk tests. To test the relationship between albuterol dosage and both bolus volume and PICU length of stay, we used gamma regression with a log link function, which takes the non-normality of the outcome variables into account. To test the association between albuterol dosage and number of adjuncts required, we analyzed Poisson regression models. Coefficients from all gamma and Poisson models have been exponentiated to reflect the risk ratio (or ratio of arithmetic means); values greater than one indicate that the variable is

associated with longer length of stay or a greater number of adjuncts, while values less than one indicate that the variable is associated with shorter length of stay or fewer adjuncts. Moreover, marginal means and standardized mean differences (SMD) are reported for dosage, in order to evaluate effect size. Model fit for all models was verified using goodness of fit tests. For all three outcome measures, we first assessed the univariate associations of a number of potential confounders, in addition to albuterol dosage. We then built multivariable models using backward stepwise selection with Akaike's Information Criterion (AIC, a measure of goodness of fit of the model) as the exit criterion; to avoid problems with multicollinearity, bolus volume and number of boluses were assessed in separate models. The data contained no missing information for any of the patients.

Analyses were performed in SAS (version 9.3; SAS Institute, Cary, NC). Two-sided p-values < 0.05 were used to judge statistical significance.

RESULTS

A total of 632 patients were analyzed—342 received 10 mg/hr and 290 received 25 mg/hr. Baseline characteristics are shown in Table 1. Patients in both groups had similar asthma severity at the time of PICU admission, while those receiving 25 mg/hr were slightly older. The frequency of 10 mg/hr albuterol use differed over time, with its use being uncommon during 2011 and increasing to become the predominant form used by the end of the study (see online supplement Table S1). ACS at ICU admission and adjunctive therapy use were similar between groups within each study year (see online supplement Tables S1 and S2).

Fluid resuscitation was greater for those who received 25 mg/hr, and this difference persisted even when adjusting for initial ACS and other potential confounders (Tables 2 and 3). In univariate analysis, this difference was only seen for ICU fluid boluses, not pre-ICU (Table 2). In multivariable analysis (Table 3), even after controlling for other factors, mean bolus volume was 50.03 ml/kg (95% CI, 44.23-56.59), in the 25 mg/hr albuterol dose group compared with 42.64 ml/kg (95% CI, 37.80-48.10) in the 10 mg/hr group, or 17% greater (RR:1.17, 95% CI, 1.07-1.29, small effect size of SMD=0.20). Other factors also associated with increased use of fluid resuscitation included ACS on PICU admission and number of adjuncts, while volume was decreased for older patients. For each specific number of adjunctive therapies received, patients receiving 25 mg/hr albuterol required a higher volume of fluid resuscitation than those receiving 10 mg/hr (online supplement Table S3).

Albuterol dose was not significantly associated with the total number of adjunctive therapies per patient in univariate analysis (Table 1 and 4) or when controlling for confounding variables such as illness severity (Table 4) although more children treated with lower dose albuterol received at least one adjunctive therapy during their treatment course. There were significant differences in use of specific therapies, with patients receiving lower dose albuterol more frequently receiving magnesium and patients receiving higher dose albuterol more frequently receiving terbutaline (Table 1). More patients receiving lower dose albuterol were given adjunctive IV magnesium prior to ICU admission (Table 1). While the frequency of ICU magnesium use did not differ by albuterol dosage, patients who received lower dose albuterol were more likely to receive a continuous IV infusion of magnesium than those receiving higher dose albuterol (Table 1). More patients in the 25 mg/hr group received intramuscular epinephrine (137 (47%) vs 95 (28%); $p<0.001$), with this therapy exclusively used in the emergency department prior to PICU admission. Factors associated with use of more adjuncts in multivariable analysis included ACS, PICU length of stay, and bolus volume (Table 4).

The use of higher dose albuterol was not associated with shorter PICU stays. In fact, mean length of stay was 2.28 days (95% CI, 2.05-2.54) in the 10 mg/hr group compared to 2.74 days (95% CI, 2.45-3.05) in the 25 mg/hr group (RR: 1.20, CI 1.10-1.31, small effect size of SMD=0.16) (Tables 2 and 5). Importantly, this difference remained after adjusting for admission ACS. Other things associated with increased PICU length of

stay in multivariable analysis were higher ACS on PICU admission, higher fluid bolus volume, and increased number of adjuncts.

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DISCUSSION

In this study of 632 patients receiving continuous albuterol in the PICU, we found that the use of 10 mg/hr albuterol was associated with the administration of less fluid resuscitation without the need for an increased number of adjunctive therapies when compared to 25 mg/hr. Higher dose continuous albuterol was associated with a 17% increase in fluid bolus needs when adjusting for important covariates. Despite less hemodynamic toxicity (as measured by fluid resuscitation) and no difference in median number of adjuncts per patient, receiving 10 mg/hr albuterol was actually associated with a shorter length of stay compared to 25 mg/hr despite similar illness severity, although it is important to realize that this was not an efficacy study so we cannot determine whether albuterol dose was the cause of this change.

Our findings mirror those of other recent pediatric studies suggesting significant side effects associated with continuous albuterol, specifically tachycardia and hypotension, raising concern for cardiac toxicity associated with this therapy (6, 7, 9). While Phumeetham et al have argued for the lack of real cardiovascular toxicity at even very high doses of albuterol (75-150 mg/hr), other studies have demonstrated clear cardiac toxicity in β -agonist-associated diastolic hypotension and have shown that fluid resuscitation can reduce this risk (6, 7, 13). While the short- and long-term effects of albuterol-related hypotension are uncertain, it seems unlikely that sustained hypotension (of any cause) should go untreated.

There are some strengths of this study that should be highlighted. It is a large study in a busy quaternary children's hospital. We included all patients who met straightforward inclusion criteria, which could limit our risk for selection bias. In addition, our primary outcome is simple, objective, and easy to understand. The administration of fluid boluses may indicate a clinically relevant hemodynamic outcome better than merely identifying a vital sign change, but further prospective studies are needed to confirm this suspicion. Given our large sample size, we were better able to account for confounders than previous pediatric studies investigating the hemodynamic impact of continuous albuterol (7).

Our study has several limitations due to its retrospective nature and single center scope. Since the data were obtained via retrospective chart reviews, the specific indication for fluid resuscitation and vital signs at the time of fluid boluses are frequently unavailable. It is possible that fluid boluses were given for reasons other than hemodynamic instability. In addition, fluid administration was not protocolized but was at the discretion of the treating physician, so the bolus could vary between patients. We did identify an association between fluid resuscitation volume and need for adjuncts and increased length of stay. We suspect that this association is an effect of illness severity and intensity of treatment rather than due to the fluid resuscitation causing clinical worsening. Some fluid resuscitation occurred in the emergency department prior to initiation of continuous albuterol. The number and volume of fluid boluses administered in the emergency department did not differ between the two albuterol dosages.

Although the reasons for this are unclear, we suspect it may be due to the limited time

patients are exposed to continuous albuterol and other asthma therapies prior to PICU admission.

The choice of 10 or 25 mg/hr albuterol was made by the treatment team based, in part, on their assessment of the patient and their personal experience with continuous albuterol. However, the primary driver for selection of a specific albuterol dosage appears to be clinical awareness of the lower dose option rather than disease severity. We did not have weight or body mass index data available for our analysis so we are unable to evaluate the impact of weight-based dosing on fluid resuscitation needs. Also, the addition of other therapies was also at the discretion of the clinical team managing the patient. While our unit has an asthma treatment guideline that was unchanged over the study period, the specific therapies prescribed were ultimately decided by the treating physician, and some practices did tend to shift over the study period. The use of terbutaline declined over the study period while the use of magnesium increased. This reduction in terbutaline use likely reflects increased attention to the cardiovascular side effects commonly associated with terbutaline, but the overall terbutaline use was very low (9 patients total out of 632) and not associated with overall fluid use. We also saw a rise in magnesium administration in the ED over time potentially due to growing evidence that magnesium may reduce hospitalization, although this seems unlikely to be related to differences in fluid resuscitation since this difference was primarily seen after ICU admission rather than in the ED (14-16).

An important limitation is that our specific asthma treatment practices likely differ from some other centers, thus limiting the generalizability of our results. Our magnesium use (71% overall) is likely higher than some centers, although prior studies have reported rates > 60% (4). We suspect that much of our higher magnesium use may be due to increasing ED use over time, as previously discussed. Additionally, magnesium was not associated with increased fluid needs, and indeed the increased magnesium occurred in the setting of decreasing fluid needs, which suggests magnesium use should not impact the generalizability of our primary outcome. Our NIV use in both dose groups was also higher than what is used in many centers. The literature suggests minimal effect on hemodynamics, so variability in NIV use should also not limit the generalizability of our primary outcome (17). Our use of invasive mechanical ventilation and terbutaline were much lower than what is described in the PICU literature—a finding that could result in lower rates of hypotension and need for fluid resuscitation in our cohort and somewhat limit the generalizability to those units with high intubation rates and terbutaline usage (4, 18).

CONCLUSION

Compared to those receiving higher-dose continuous albuterol, children who received 10 mg/hr of albuterol received less fluid resuscitation without an increased need for other adjunctive therapies, even when adjusting for important confounders. Given the growing concerns for cardiovascular toxicity of continuous albuterol in this population and data such as our suggesting that higher doses may not be helpful, prospective studies evaluating dosing of continuous albuterol in pediatric status asthmaticus should be done. These should include more explicit evaluation of hypotension, specific guidelines for fluid resuscitation, and evaluation of markers of myocardial toxicity to determine the true impact of continuous albuterol dose on outcomes in status asthmaticus. Since status asthmaticus is a leading cause of health-related disability and hospitalization for children, this represents an important target for improving outcomes and reducing morbidity in critically ill children with asthma.

ACKNOWLEDGEMENTS

AL, MMC, and TK contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. The authors would like to thank Thomas Chovanec and Jennifer McKenzie for their help in setting up the automated data collection program to identify our study patients. Special thanks also to Dr. Mark Hall and Dr. Elizabeth Allen for their thoughtful review of our manuscript.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1: Patient characteristics and adjunctive treatment. Data are expressed either as n (%)¹ or median (IQR)². Statistical comparisons were performed using either chi-square/Fisher's exact tests and Wilcoxon-Mann-Whitney tests

Characteristic	Dosage		
	10 mg (n=342)	25 mg (n=290)	p-value
<i>Demographics</i>			
Female	161 (47)	125 (43)	0.421
Age	5 (3-8)	6 (3-10)	0.026
ACS at ICU Admit	6 (5-8)	6 (5-7)	0.403
<i>Adjuncts</i>			
NIV	200 (58)	162 (55)	0.507
Invasive ventilation	8 (2.3)	9 (3.1)	0.554
Heliox	13 (3.8)	7 (2.4)	0.321
Aminophylline	6 (1.8)	12 (4.1)	0.073
Ketamine	26 (7.6)	29 (10)	0.287
Infusion ³	16 (62)	23 (79)	0.23
Magnesium	256 (74)	191 (65)	0.013
Pre-ICU ⁴	182 (53)	129 (44)	0.031
ICU ⁴	167 (49)	126 (43)	0.174
Infusion ⁴	138 (40)	92 (32)	0.025
Terbutaline	1 (0.3)	8 (2.8)	0.014

¹Absolute frequency (relative frequency)

²Interquartile range

³Expressed as percentage of patients treated with ketamine

⁴Expressed as percentage of patients treated with magnesium

Table 2: Clinical outcomes including comparison of LOS and bolus fluid resuscitation. Data are expressed as median (IQR)¹ unless otherwise specified. Statistical comparisons were performed using either chi-square/Fisher's exact tests and Wilcoxon-Mann-Whitney tests

Characteristic	Dosage		
	10 mg (n=342)	25 mg (n=290)	p-value
Hospital LOS	3.2 (2.4-4.4)	3.7 (2.8-5.6)	<0.001
PICU LOS	1.8 (1.2-2.8)	2.0 (1.4-3.1)	0.033
Number of Adjuncts	1 (1-2)	1 (1-2)	0.187
At Least One Adjunct ¹	302 (88.3)	234 (80.69)	0.008
More than Two Adjuncts ¹	33 (9.65)	32 (11.03)	0.568
Number of boluses	2 (1-3)	2 (1-4)	0.002
Pre-ICU	1 (1-1.5) [mean 1.1]	1 (1-2) [mean 1.1]	0.521
ICU Only	1 (0-2) [mean 1.3]	1 (0-3) [mean 1.7]	0.006
Total bolus volume (ml/kg)	40 (20-60) [mean 44 ml/kg]	40 (20-70) [mean 52 ml/kg]	0.011

¹Intraquartile Range

²Data expressed as absolute frequency (relative frequency)

Table 3: Factors associated with greater fluid bolus volume including univariate and adjusted analyses using gamma regression with a log link function.

Variable	Univariate Association			Adjusted Association		
	Risk Ratio	95% CI ¹	p-value	Risk Ratio	95% CI	p-value
Albuterol: 25 mg vs. 10 mg	1.1908	(1.0770, 1.3167)	0.001	1.1732	(1.0651, 1.2921)	0.001
Age (years)	0.9958	(0.9819, 1.0031)	0.467	0.9863	(0.9757, 0.9970)	0.012
ACS	1.0542	(1.0204, 1.0684)	<.001	1.0300	(1.0056, 1.0551)	0.016
Hospital LOS (d ²)	1.0188	(1.0013, 1.0210)	0.009	excluded ³		
PICU LOS (d)	1.0698	(1.0284, 1.0696)	<.001	excluded ³		
Number of Adjuncts	1.2000	(1.1453, 1.2516)	<.001	1.1920	(1.1377, 1.2488)	<.001
Epinephrine	1.1307	(1.0192, 1.2543)	0.020	1.0955	(0.9897, 1.2125)	0.079
Ipratropium Bromide	1.2927	(1.0222, 1.6348)	0.032	1.2710	(1.0196, 1.5845)	0.033

¹95% Confidence Interval

²Days

³Excluded due to negligible effect on model performance.

Table 4: Factors associated with an increased number of adjuncts used including univariate and adjusted analyses using Poisson regression. Data are reported as risk ratios

Variable	Univariate Effects			Adjusted Effects		
	Risk Ratio	95% CI ¹	p-value	Risk Ratio	95% CI	p-value
Albuterol: 25 mg vs. 10 mg	0.9666	(0.8493, 1.1000)	0.606	0.8962	(0.7862, 1.0215)	0.101
Age (years)	1.0173	(1.0034, 1.0316)	0.015	1.0111	(0.9968, 1.0254)	0.130
ACS	1.0869	(1.0543, 1.1205)	<.001	1.0530	(1.0201, 1.0868)	0.001
Hospital LOS (d ²)	1.0253	(1.018, 1.0327)	<.001	excluded ³		
PICU LOS (d)	1.0843	(1.0674, 1.1014)	<.001	1.0651	(1.0466, 1.084)	<.001
Number of Boluses	1.1223	(1.0933, 1.1521)	<.001	excluded ³		
Bolus Volume	1.0057	(1.0043, 1.0071)	<.001	1.0043	(1.0028, 1.0058)	<.001
Epinephrine	1.1177	(0.9798, 1.2752)	0.098	excluded ³		
Ipratropium Bromide	0.9555	(0.7104, 1.2852)	0.764	excluded ³		

¹95% Confidence Interval

²Days

³Excluded due to negligible effect on model performance.

Table 5: Factors associated with longer PICU length of stay (days) including both univariate and adjusted analyses using gamma regression with a log link function.

Variable	Univariate Association			Adjusted Association		
	Risk Ratio	95% CI ¹	p-value	Risk Ratio	95% CI	p-value
Albuterol: 25 mg vs. 10 mg	1.1990	(1.0821, 1.3286)	0.001	1.1995	(1.1019, 1.3058)	<.001
Age (years)	1.0147	(1.0033, 1.0262)	0.012	excluded ²		
ACS	1.0926	(1.0664, 1.1195)	<.001	1.0483	(1.0266, 1.0704)	<.001
Number of Boluses	1.1061	(1.0791, 1.1337)	<.001	excluded ²		
Volume of Boluses (ml/kg)	1.0048	(1.0035, 1.0061)	<.001	1.0016	(1.0005, 1.0028)	<.001
Number of Adjuncts	1.4150	(1.3570, 1.4754)	<.001	1.3664	(1.3081, 1.4273)	0.006
Epinephrine	0.9784	(0.8792, 1.0889)	0.690	0.8684	(0.7950, 0.9485)	0.002
Ipratropium Bromide	0.7529	(0.5914, 0.9586)	0.021	0.7773	(0.6392, 0.9453)	0.012

¹95% Confidence Interval

²Excluded due to negligible effect on model performance.