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Oral Nutrition During Continuous Albuterol for Pediatric Critical Asthma: A Matched Cohort Study

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ABSTRACT

Purpose: The practice of withholding oral nutrition for children hospitalized for critical asthma receiving continuous albuterol is not evidence based. We sought to characterize oral nutrition practices in this population and estimate the frequency of aspiration-related respiratory failure.
Methods: We performed a single-center retrospective, matched cohort study of children 3–17 years of age admitted to a pediatric intensive care unit from Oct 2020 to May 2023 for critical asthma receiving continuous albuterol. Cases provided oral nutrition were matched 1:2 to controls withheld nutrition by age and National Heart Lung and Blood Institute asthma severity classification. The primary outcome was aspiration-related respiratory failure defined as any respiratory support escalation following observed aspiration. Descriptive data included demographics, anthropometrics, pediatric asthma severity scores, adjunct asthma interventions, continuous albuterol duration, mortality, and length of stay.
Results: Of 36 cases and 72 matched controls, the mean age was 9.1±3.9 years and 66.7% had moderate-severe persistent asthma. Cases and controls had comparable anthropometrics and admission pediatric asthma severity scores. No aspiration-related respiratory failure events were observed even among those receiving nutrition concurrent to noninvasive ventilation. Compared to controls, cases experienced a longer continuous albuterol duration (median: 1.1 [interquartile range: 0.7–1.8] versus 0.7 [interquartile range: 0.3–1.3] days, $p<0.001$). No differences in length of stay, adjunct interventions, endotracheal intubation rates, and mortality were observed between cases and controls.
Conclusion: For children hospitalized for critical asthma, oral nutrition during continuous nebulized albuterol appeared well tolerated. While prospective validation is required, the practice of withholding oral nutrition for continuous albuterol administration may be unwarranted.

Keywords: Status asthmaticus; Respiratory aspiration; Enteral nutrition

Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Guidelines from the Society of Critical Care Medicine (SCCM) and the Association for Parenteral and Enteral Nutrition recommend the provision of early enteral nutrition for children hospitalized with critical illness without an absolute contraindication [1]. In the pediatric intensive care unit (PICU) setting, many children hospitalized for pulmonary pathology undergo noninvasive respiratory support (e.g., supplemental oxygen and non-invasive ventilation) and will have oral nutrition withheld until off such support or a clear improvement in clinical trajectory is observed [2,3]. This practice stems from a perception that a child in respiratory distress who is orally fed during noninvasive respiratory support is at increased risk of oral dysphagia, aspiration events, and, at worst, aspiration-related respiratory failure prior to or during induction for endotracheal intubation [4,5]. Children admitted to the PICU for an acute asthma exacerbation, referred to as having 'critical asthma', are routinely treated with continuous nebulized albuterol delivered through a variety of nasal and facial mask interfaces [6]. To date, no reports have estimated the frequency of aspiration-related respiratory failure in this population or characterized patients who did or did not experience oral nutrition intolerance.

To address these knowledge gaps, we performed a single-center, retrospective observational matched cohort study among children hospitalized in the PICU for critical asthma receiving continuous nebulized albuterol. We sought to characterize oral nutrition practices in this population and explore for features that may contribute to the risk of aspiration-related respiratory failure by comparing cohorts with and without oral nutrition exposure while receiving continuous albuterol. We hypothesized that no differences in the aspiration-related respiratory failure rates will be observed among children with and without oral nutrition exposure.

MATERIALS AND METHODS

Study design and sampling criteria

We performed a single-center, retrospective matched cohort study from October 2020 through May 2023 including patient encounters hospitalized in a 28-bed PICU within a 313-bed quaternary pediatric referral center. Inclusion criteria were patient age at admission between 3 through 17 years of age, the primary admission diagnosis of critical asthma and concurrent treatment with nebulized continuous albuterol. The diagnosis of critical asthma has previously been described and is defined here as an acute asthma exacerbation receiving a minimum of intravenous systemic corticosteroids, continuous albuterol, and PICU-level monitoring [7]. Exclusion criteria included parenteral nutrition dependency or enteral nutrition delivered through a nasoenteric or gastrostomy tube. This study was reviewed and approved by the Johns Hopkins All Children's Hospital Institutional Review Board (IRB) which permitted a waiver of consent (IRB #00327155).

Data source and matching criteria

Encounters with critical asthma were identified using an internal data warehouse query. All research data were then manually extracted from the electronic health record. 'Cases,' defined as those children with critical asthma who received oral nutrition concurrent to continuous albuterol administration, were identified and matched at a ratio of 1:2 to 'controls' withheld nutrition during exposure to continuous albuterol. Matching criteria included patient age at admission ±1 year and exact National Heart Lung and Blood Institute

(NHLBI) Asthma Severity classification. Children provided oral nutrition were given observed breaks off face-mask, bilevel positive airway pressure (BiPAP) masks or nasal-cannula interfaces sufficient to offer by mouth nutrition.

Study outcomes and definitions

The primary study outcome was the frequency of oral nutrition administration concurrent to continuous albuterol administration. Descriptive features included the timing of oral nutrition initiation, gender-adjusted anthropometric data (e.g., gender adjusted weight-for-age *z*-scores), presence of malnutrition including severity classification (mild=body mass index [BMI] *z*-score [−1 to −1.9], moderate=BMI *z*-score [−2 to −2.9], severe=BMI *z*-score [−3 or less]), and comorbid overweight or obesity status (overweight=BMI 85–95th percentile for age, obese=BMI 95th percentile for age or BMI≥30 whichever is lower, severe obesity=BMI≥99th percentile for age or BMI≥35) [8,9]. The secondary study outcome was aspiration-related respiratory failure defined as an escalation of respiratory support immediately following a documented clinical aspiration event (e.g., escalation to non-invasive positive pressure ventilation or transition to invasive mechanical ventilation). Additional descriptive data included demographics, severity of illness indices (e.g., Pediatric Index of Mortality-III Risk of Mortality), admission pediatric asthma severity scores (PASS), adjunct critical asthma therapies such as high-flow nasal cannula (HFNC), BiPAP, continuous positive airway pressure, invasive mechanical ventilation, aminophylline, terbutaline, heliox, continuous albuterol duration, hospital length of stay (LOS), extracorporeal life support, or in-hospital mortality.

Statistical analysis

Throughout the manuscript, data are reported as proportions with percentages, means with standard deviations, or medians with interquartile range (IQR) as indicated by data type and distribution normality (assessed via Kolmogorov–Smirnov testing). Nutritional, clinical, and descriptive data between cohorts with and without oral nutrition concurrent to continuous albuterol administration were compared using student's *t*-test or Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Paired statistics were performed, where appropriate. Missing data were not imputed. All statistical analyses were two-sided, and type I error was set at 0.05. All analyses were performed by using Stata version 13.1 software (StataCorp).

RESULTS

Study sample and cohort characteristics

During the study period, we identified 36 cases that were matched to 72 controls that met all study criteria accounting for a total sample size of 108 participants. Demographics, admission data, and asthma-specific historical features can be found in **Table 1**. Cases and controls were well matched with a mean age of 9.1±3.9 years, a majority with either moderate or severe persistent NHLBI chronic asthma classification (66.7%), and a median PASS score on PICU admission of 11 (IQR: 10–13). With regards to anthropometric data (**Table 2**), no differences in admission weight, BMI, and rates of overweight or obesity status were noted. A greater proportion of controls withheld oral nutrition during continuous albuterol administration were identified as severely obese as compared to cases who were provided oral nutrition during continuous albuterol (25% versus 5.6%, p=0.016).

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Table 1. General demographics, admission data, and asthma-specific historical data for the overal study sample including comparative analyses for cases and controls

Characteristic	Total sample (n=108)	Controls (n=72)	Cases (n=36)	*p*-value
Age (yr)	9.1±3.9	9.1±3.9	9.1±3.9	0.963
Sex				>0.999
Male	48 (44.4)	32 (44.4)	16 (44.4)	
Female	60 (55.6)	40 (55.6)	20 (55.6)	
Historically disparate race category				
Black	55 (50.9)	35 (48.6)	20 (55.6)	0.544
White	32 (29.6)	22 (30.6)	10 (27.8)	0.826
Other	21 (19.4)	15 (20.8)	6 (16.7)	0.797
Latino	17 (15.7)	11 (15.3)	6 (16.7)	>0.999
NHLBI severity category				>0.999
Intermittent	27 (25.0)	18 (25.0)	9 (25.0)	
Mild persistent	9 (8.3)	6 (8.3)	3 (8.3)	
Moderate persistent	51 (47.2)	34 (47.2)	17 (47.2)	
Severe persistent	21 (19.4)	14 (19.4)	7 (19.4)	
Prior history of atopy	53 (49.1)	40 (55.6)	13 (36.1)	0.068
Prior PICU hospitalization for asthma	31 (28.7)	23 (31.9)	8 (22.2)	0.369
Prior history of ventilation for asthma	8 (7.4)	7 (9.7)	1 (2.8)	0.264
Admission bacterial pneumonia	12 (11.1)	8 (11.1)	4 (11.1)	>0.999
Admission PASS	11 (10–13)	11 (9–13)	12 (10–13)	0.262
Admission during evening hours	61 (56.4)	41 (56.9)	20 (55.6)	>0.999

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
Cases: Patients who received enteral nutrition during continuous albuterol administration.
Controls: Patients without enteral nutrition during continuous albuterol administration.
NHLBI: National Heart Lung and Blood Institute, PICU: pediatric intensive care unit, PASS: pediatric asthma severity score.

Table 2. Anthropometric data for the overal study sample including comparative analyses for cases and controls

Characteristic	Total sample (n=108)	Controls (n=72)	Cases (n=36)	*p*-value
Weight (kg)	42.9±27.0	45.3±28.6	38.0±23.0	0.184
Age/gender *z*-score	0.9±1.6	1.1±1.6	0.5±1.5	0.116
Body mass index (kg/m^2)	21.4±7.1	22.3±7.8	19.6±5.1	0.082
Age/gender *z*-score	0.9±1.6	1.1±1.6	0.6±1.4	0.140
Malnutrition				
Any category	12 (11.1)	6 (8.3)	6 (16.7)	0.209
Mild	8 (7.4)	4 (5.6)	4 (11.1)	0.437
Moderate	2 (1.9)	0 (0)	2 (5.6)	0.109
Severe	1 (0.9)	1 (1.4)	0 (0)	>0.999
Overweight	12 (11.1)	6 (8.3)	6 (16.7)	0.209
Obesity	37 (34.2)	28 (38.9)	9 (25.0)	0.198
Severe obesity	20 (18.5)	18 (25.0)	2 (5.6)	0.016

Values are presented as mean±standard deviation or number (%).
Cases: Patients who received enteral nutrition during continuous albuterol administration.
Controls: Patients without enteral nutrition during continuous albuterol administration.

Oral nutrition data

All study subjects were offered ad lib oral nutrition during their hospital stay without enteric tube placement. As expected, cases offered oral nutrition during continuous nebulized albuterol received nutrition earlier than controls by 7.8 hours (11.1 [IQR: 0.3–23.4] versus 18.9 [IQR: 10.5–36.3] hours after PICU admission, p=0.002). While interruptions in oral nutrition (defined as nil per os order placed after initiation of oral nutrition with provider documentation of concerns of dysphagia) were more frequently documented among cases as compared to controls (16.7% versus 1.4%, p=0.005), no child was observed to have aspiration-related respiratory failure.

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Table 3. Asthma treatment and clinical data for the overal study sample including comparative analyses for cases and controls

Characteristic	Total sample (n=108)	Controls (n=72)	Cases (n=36)	*p*-value
Length of stay (d)				
Hospital	2.6 (1.8–3.6)	2.5 (1.7–3.5)	2.8 (2–3.8)	0.226
PICU	1.5 (1.0–2.6)	1.4 (0.9–2.3)	1.9 (1.2–2.9)	0.031
Continuous albuterol duration (d)	0.8 (0.5–1.5)	0.7 (0.4–1.4)	1.0 (0.6–1.7)	0.026
Adjunctive treatments				
HFNC	51 (47.2)	37 (51.4)	20 (55.6)	0.838
BiPAP	19 (17.6)	11 (15.3)	8 (22.2)	0.425
Terbutaline	27 (25.0)	14 (19.4)	13 (36.1)	0.097
Epinephrine	4 (3.7)	3 (4.2)	1 (2.8)	>0.999
Ketamine	3 (2.8)	3 (4.2)	0 (0)	0.549
Aminophylline	3 (2.8)	1 (1.4)	2 (5.6)	0.257
Heliox	0 (0)	0 (0)	0 (0)	>0.999
Volatile anesthetic gas	0 (0)	0 (0)	0 (0)	>0.999
Mechanical ventilation	0 (0)	0 (0)	0 (0)	>0.999
Mortality	0 (0)	0 (0)	0 (0)	>0.999
Extracorporeal life support	0 (0)	0 (0)	0 (0)	>0.999

Values are presented as median (interquartile range) or number (%).
Cases: Patients who received enteral nutrition during continuous albuterol administration, Controls: Patients without enteral nutrition during continuous albuterol administration.
PICU: pediatric intensive care unit, HFNC: high-flow nasal cannula, BiPAP: bilevel positive airway pressure.

Clinical trajectory data

Critical asthma-related treatments and general inpatient clinical trajectory data can be found in **Table 3**. Cases offered oral nutrition had a longer median PICU LOS (1.9 [IQR: 1.2–2.9] versus 1.4 [0.9–2.3] days, p=0.031) and a longer median duration of continuous albuterol (1.0 [IQR: 0.6–1.7] versus 0.7 [IQR 0.4–1.4] days, p=0.026). There were no differences in adjunct critical asthma treatments, invasive mechanical ventilation, mortality, or extracorporeal life support rates between cases and controls.

DISCUSSION

In this single-center retrospective, matched cohort study including children 3–17 years of age hospitalized for critical asthma, we observed no instances of aspiration-related respiratory failure including those who were provided oral nutrition concurrent to non-invasive respiratory support and other adjunct therapies for asthma in addition to continuous nebulized albuterol. While we did observe a longer PICU LOS and duration of continuous albuterol among cases as compared to controls, these statistically significant differences were likely not clinically relevant. The greater degree of acute disease severity as represented by PASS and adjunct asthma treatments did not appear to dissuade providers from prescribing oral nutrition. While we await prospective validation of our findings, we speculate that the practice of withholding oral nutrition in this population may be unwarranted.

The decision to initiate nutrition during critical illness including the route, volume, and timing is multifactorial and incorporates parental perceptions regarding the necessity of oral nutrition, provider determination of malnutrition status, and the potential risks of aspiration-related respiratory failure. Malnutrition status on admission for critically ill children has been associated with poor clinical outcomes, including higher rates of hospital-acquired infections, longer LOS, and increased index mortality rates [10-12]. As such, SCCM and American Society for Parenteral and Enteral Nutrition developed evidence-based guidelines to assist clinical providers in the provision of optimal nutritional therapies for

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critically ill children [1]. The most recent iteration, published in 2017, recommend early, oral nutrition as the preferred route to optimize gastrointestinal mucosal integrity, motility, and macronutrient intake. Still, the practice of withholding oral nutrition remains anecdotally common and driven by hesitation related to dysphagia and aspiration-related respiratory failure for children hospitalized for critical asthma receiving continuous albuterol. This the first manuscript to describe oral nutrition practices and estimate the rates of aspiration-related respiratory failure in this population.

Prior research has evaluated oral nutrition timing and practices among critically ill children with and without asthma exacerbation receiving noninvasive respiratory support such as BiPAP and HFNC [13,14]. In a retrospective study of children on BiPAP for acute infectious processes, those children started on enteral nutrition within 24 hours experienced an increased rate of achieving goal caloric and protein intake within 72 hours [15]. In our study, children with critical asthma who received oral nutrition during continuous albuterol administration received nutrition at a median difference of 7.8 hours earlier when compared to the controls withheld because of concurrent continuous albuterol application. In a retrospective cohort study analyzing nutrition characteristics during BiPAP exposure for critical asthma, there were no recorded instances of adverse effects, including aspiration, emesis, increased work of breathing, invasive mechanical ventilation, or acute removal of the BiPAP mask [13]. These data are consistent with our results that revealed no aspiration-related respiratory failure. In our study sample, 25% of those provided oral nutrition did so during brief observed breaks off BiPAP.

In recent years, several reports have corroborated the concept of oral nutrition safety among children receiving noninvasive respiratory support for bronchiolitis. A retrospective cohort study from 2017, showed that of the 132 children admitted with bronchiolitis on HFNC, only one patient had aspiration-related respiratory failure [16]. In a similarly designed observational report, children admitted with bronchiolitis on HFNC who received oral nutrition experienced shorter time to discharge by 10 hours [17]. In our study sample, 19% of those cases receiving oral nutrition had a concurrent prescription of continuous albuterol nebulized through a HFNC circuit without aspiration-related respiratory failure.

Limitations

The study findings herein represent a single-center experience and are generalizable to similar patient care settings such as quaternary pediatric referral centers. The indication for initiating oral nutrition and whether an assessment related to oral dysphagia was not documented sufficiently in the electronic health record for analysis in this report. As the only route of nutrition studied was oral, we cannot assume the necessity or safety of nasoenteric tube placement and feeding in this population and context. The LOS observed for our cohort was brief for both cases and controls; consistent with national estimates for pediatric critical asthma (e.g., 75% of our sample was hospitalized for <3.6 days). Yet, this brief LOS prevents our analyses of “early” nutrition benefit as compared to “delayed” nutrition initiation. This study was not powered to assess differences in clinical outcomes because of oral nutrition exposure and our descriptive comparisons related to clinical trajectory are thus exploratory. The etiology of observed differences in LOS and duration of albuterol could be related to breaks off of continuous albuterol to provide enteral nutrition. Yet, in our experience the breaks to allow a child to take oral nutrition are extremely brief and are unlikely to explain these findings alone. Finally, no qualitative data were documented to understand provider and parental perceptions regarding the necessity and timing of nutrition during continuous

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albuterol administration. Given the need for prospective validation of these findings, the evaluation of perceived delay from parents and caregivers represents an exciting area for future inquiry.

Conclusions

In this matched cohort study of critically ill children hospitalized for acute asthma exacerbation receiving continuous nebulized albuterol, we observed no evidence of clinically symptomatic aspiration or aspiration-related respiratory failure for cases offered oral nutrition. While we recommend a period of observation to determine clinical trajectory, the practice of withholding oral nutrition because of continuous albuterol administration in this population is likely unnecessary. Future research should include qualitative inquiry of the multidisciplinary care team and parental perceptions regarding oral nutrition initiation.

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