RESEARCH ARTICLE

Adjunctive Pharmacotherapies in Children With Asthma Exacerbations Requiring Continuous Albuterol Therapy: Findings From The Ohio Pediatric Asthma Repository

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ABSTRACT

OBJECTIVES: To identify associations between use of ipratropium and/or intravenous magnesium and outcomes of children hospitalized with acute asthma exacerbations and treated with continuous albuterol.

METHODS: Secondary analysis of data from children prospectively enrolled in the multicenter Ohio Pediatric Asthma Repository restricted to only children who were treated with continuous albuterol in their initial inpatient location. Children were treated with adjunctive therapies per the clinical team.

RESULTS: Among 242 children who received continuous albuterol, 94 (39%) received ipratropium only, 13 (5%) received magnesium alone, 42 (17%) received both, and 93 (38%) received neither. The median duration of continuous albuterol was 7.0 (interquartile range [IQR]: 2.8–12.0) hours. Ipratropium use was associated with a shorter duration of continuous albuterol (4.9 [IQR: 2.0–10.0] hours) compared with dual therapy (11.0 [IQR: 5.6–28.6] hours; $P = .001$), but magnesium use was not (7.5 [IQR: 2.5–16.0] hours; $P = .542$). In Cox proportional models (adjusted for hospital, demographics, treatment location, and respiratory failure), magnesium was associated with longer durations of continuous albuterol (hazard ratio, 0.54 [95% confidence interval: 0.37–0.77]; $P < .001$) and hospitalization (hazard ratio, 0.41 [95% confidence interval: 0.28–0.60]; $P < .001$), but ipratropium was not.

CONCLUSIONS: Ipratropium and magnesium were both often used in children with severe asthma hospitalizations that required continuous albuterol therapy. Magnesium use was associated with unfavorable outcomes, possibly reflecting preferential treatment to patients with more severe cases and differing practices between centers. Given the high prevalence of asthma, wide variations in practice, and the potential to improve outcomes and costs, prospective trials of these adjunctive therapies are needed.

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Asthma is the most common chronic illness in childhood, affecting ~10% of all children.[1,2] Asthma exacerbations frequently prompt hospitalization, with ~150 000 pediatric asthma admissions occurring in the United States annually.[3] Severe asthma exacerbations (sometimes termed "status asthmaticus" or "critical asthma") are a common indication for admission to a PICU.[4–6] Standard therapies are systemic corticosteroids and continuous nebulization of β-agonist bronchodilators (eg, albuterol), along with the consideration of adjunct therapies.[7]

Two suggested adjunct therapies are inhaled ipratropium and intravenous magnesium.[7] Ipratropium is an anticholinergic bronchodilator that has been shown to improve clinical outcomes when administered in the emergency department to children with asthma exacerbations.[8] However, the administration of ipratropium has not been shown to improve outcomes of children admitted to the general ward of the hospital with asthma.[9,10] Currently, there are no data to support or refute the efficacy of ipratropium among more severely ill subjects requiring PICU admission and treatment with continuous nebulization of albuterol. Currently, ~70% of PICU patients with status asthmaticus in the United States receive ipratropium, but use varies widely between centers.[11] The lack of data with respect to the use of ipratropium in the ICU setting is reflected in marked variation in care practices. Among the 14 children's hospitals that contribute data to either the Collaborative Pediatric Critical Care Research Network (CPCCRN) or the Ohio Pediatric Asthma Repository (OPAR), ipratropium use in individual centers ranges from <20% to >80% of PICU patients with asthma.[11,12]

Intravenous magnesium has similarly been shown to have efficacy in pediatric emergency department patients, but there are no randomized controlled trials of magnesium in pediatric inpatients with asthma.[13–16] In 1 small observational study, use of magnesium in 19 PICU patients with critical asthma was associated with improved respiratory rates.[17] In the United States, magnesium is prescribed to ~40% of PICU asthma patients, and use within the 8 CPCCRN PICUs ranged from 23% to 64%.[11]

Use of both ipratropium and magnesium in PICU patients with severe acute asthma varies widely between centers with little supportive data, including an absence of robust retrospective studies. If these drugs are efficacious, then outcomes could be improved by increasing usage, especially in PICUs with low treatment rates. Alternatively, if these drugs are not associated with improved outcomes, limiting prescription could reduce costs and the risk of adverse effects. In this article, we present a secondary analysis of the multicenter OPAR study in which children admitted for asthma exacerbations to any of the 6 major children's hospitals in Ohio are prospectively enrolled.[12] Among the OPAR subjects, we tested for associations between clinical outcomes and the use of ipratropium and/or magnesium in pediatric inpatients with severe asthma exacerbations who were treated with continuous albuterol. We hypothesized that both drugs would be associated with a shorter duration of continuous albuterol therapy. Some of the results of this study have been previously reported in the form of an abstract[18] and in the original description of the OPAR cohort.[12]

METHODS

The institutional review board of the University Hospitals of Cleveland approved this secondary analysis. Methods for the creation of the OPAR database, which included parental consent, have been previously described.[12] Briefly, children aged 2- to 17-years-old admitted for an asthma exacerbation to 1 of 6 Ohio children's hospitals (Akron Children's Hospital, Cincinnati Children's Hospital Medical Center, Dayton Children's Hospital, Nationwide Children's Hospital [Columbus], ProMedica Toledo Children's Hospital, and Rainbow Babies and Children's Hospital [Cleveland]) were eligible for inclusion. Subjects with chronic lung disease other than asthma, hyper immunoglobulin E syndrome, cancer, or sickle cell crisis were excluded. Data were prospectively obtained from parental questionnaires and the patient's medical record; all data were subsequently validated, with any errors or discrepant data clarified, before inclusion in the database.

We present a secondary analysis that includes only patients who were treated with continuously nebulized albuterol immediately on admission to the hospital from December 2012 to September 2013. We excluded all subjects who were initially treated with intermittent albuterol at the time of hospital admission, even if they were treated with continuous albuterol later in their hospitalization. The variables that we extracted for this analysis included age, sex, weight, race and/or ethnicity, gestational age, and initial inpatient location (PICU or general ward). Administration of ipratropium and/or magnesium in the initial inpatient location was recorded. Patients were divided into 4 groups: no adjunctive therapy, ipratropium only, magnesium only, and dual therapy (ipratropium and magnesium). Drug administration before inpatient admission was not evaluated. Respiratory failure was defined as use of high-flow nasal cannula (HFNC),[19] noninvasive positive-pressure ventilation (NIPPV), or invasive mechanical ventilation (IMV).

Rates of categorical variables were compared between treatment groups by using a χ^2 analysis. Continuous variables were compared by using Kruskal-Wallis analysis of variance (ANOVA) with Dunn's test. The primary outcome was the duration of continuous albuterol treatment. Secondary outcomes were the interval from hospital admission until the time at which the patient was able to go 4 hours without albuterol ("time to q4 albuterol"), and hospital length of stay (LOS). Kaplan-Meier survival plots were created for each outcome for each of the 4 treatment groups. For each outcome, an unadjusted Cox proportional hazards model was created against the 2 treatments only as predictors. In the Cox proportional hazards models, children receiving ipratropium were compared with children who did not receive ipratropium and children receiving magnesium were compared with children who did not receive magnesium. We

assumed in these models a separate hazard baseline for each hospital, thereby adjusting for treatment center. Other independent variables were then introduced into the model 1 at a time. If the *P* value for that independent variable was <.10, it was included in the adjusted Cox proportional hazards model. For both models, results are shown as hazard ratios (HRs) with 95% confidence intervals (CIs). For both models, an HR <1 represents a longer time until the outcome. Other data are shown as *n* (%) or median (interquartile range [IQR]).

RESULTS

Out of 1012 children enrolled in OPAR during the study period, 242 children with acute asthma exacerbations were treated with continuous albuterol and were included in this analysis (Fig 1). As seen in Table 1, most (60.3%) subjects were boys and nearly half (49.2%) were African American. The median age was 6.5 (IQR: 4.0–10.4) years. More than one-third (38.8%) received ipratropium only in the initial inpatient location, 5.4% received magnesium alone, 17.4% received both, and 38.4% received neither. There was marked variation in rates of use of both therapies of interest among the participating hospitals (Fig 2). Patients receiving both medications were older than those receiving neither or ipratropium alone. Less than one-fifth of patients (45 [IQR: 18.6%]) had respiratory failure; 28 children were treated with NIPPV (1 of whom also required IMV), and 19 were treated with HFNC (including 2 subjects who received both HFNC and NIPPV).

The median duration of continuous albuterol was 7.0 (IQR: 2.8–12.0) hours (Table 2). Ipratropium alone was associated with a shorter duration of continuous albuterol (4.9 [IQR: 2.0–10.0] hours) compared with dual therapy (11.0 [IQR: 5.6–28.6] hours; $P = .001$), but the duration of continuous albuterol among magnesium only subjects (7.5 [IQR: 2.5–16.0] hours) did not differ significantly compared with those receiving dual therapy ($P = .542$). No adjunct therapy (7.0 [IQR: 3.5–10.4] hours) differed significantly compared with dual therapy ($P = .039$) but not compared with either ipratropium or magnesium alone (both $P > .5$). The median time to q4 albuterol was 38.7 (IQR: 24.9–64.6) hours. Time to q4 albuterol was shorter in patients given no adjunct compared with each of the 3 other groups individually ($P < .02$ for each comparison). Ipratropium alone was associated with a shorter time to q4 albuterol than dual therapy ($P = .001$), but magnesium alone did not differ from dual therapy ($P = .099$). The median LOS was 49.0 (IQR: 32.0–77.7) hours. Both ipratropium only (57.7 [IQR: 41.1–79.1] hours) and magnesium only (57.0 [IQR: 42.3–83.8]) were associated with longer LOS than no therapy (33.7 [IQR: 26.8–45.2] hours; $P < .02$ for both). Ipratropium only was associated with a shorter LOS compared with dual therapy (77.3 [IQR: 50.8–104.4] hours; $P = .018$), but magnesium alone was not ($P = .408$). The Kaplan-Meier plots for each outcome are shown in Fig 3.

In the Cox proportional hazards models, use of each drug was compared individually with children who did not receive that drug. In the initial Cox proportional hazards models (adjusted for hospital but no other variables), magnesium administration was associated with a significantly longer duration of continuous albuterol (HR, 0.54 [95 % CI: 0.37–0.77]), but ipratropium was not (HR, 0.96 [95% CI: 0.59–1.56]). Both magnesium (HR, 0.41 [95% CI: 0.28–0.59]) and ipratropium (HR, 0.61 [95% CI: 0.37–0.98]) were significantly associated with longer time to q4 in the unadjusted model. Magnesium (HR, 0.44 [95% CI: 0.30–0.63]) was significantly associated with longer hospital LOS, but ipratropium (HR, 0.82 [95% CI: 0.50–1.33]) was not in the unadjusted model.

Sex, race and/or ethnicity, treatment location, and respiratory failure were all included as covariates in the adjusted Cox proportional hazards models (Table 3). After adjusting for these variables, the associations between adjunct therapies and outcomes were similar to the initial model. Magnesium was associated with increased durations for all 3 outcomes. Ipratropium was associated with a longer time to q4 albuterol but not with longer durations of continuous albuterol or longer hospital LOS.

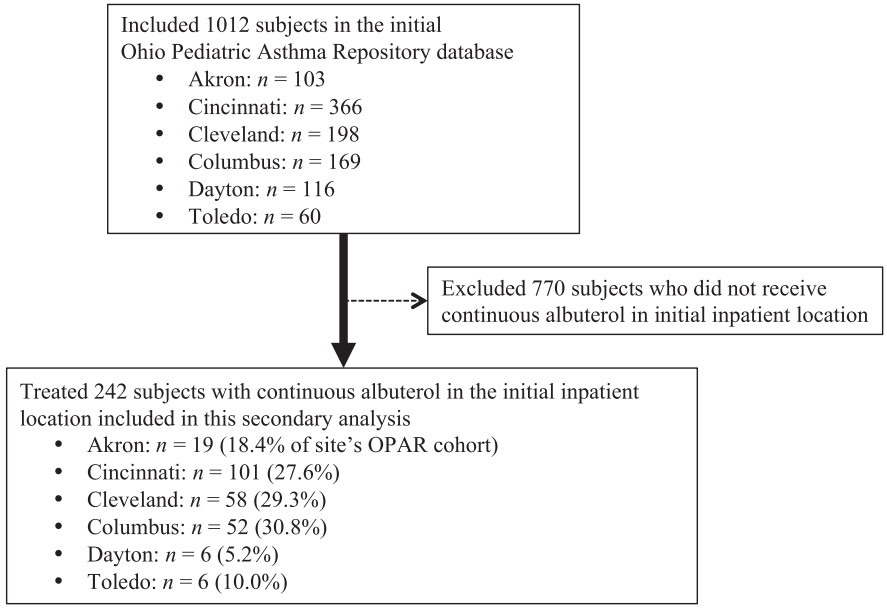

FIGURE 1 Flowchart of subjects included in the original OPAR database and subjects included in this secondary analysis.

DISCUSSION

In this secondary analysis of a prospective study of pediatric inpatients treated for severe acute asthma exacerbations with continuous albuterol, adjunctive therapy with intravenous magnesium was associated with a longer duration of continuous albuterol, but adjunctive therapy with ipratropium was not. Adjusting for

TABLE 1 Demographics of All Subjects and of Each Treatment Group

Variable	All Subjects ($N = 242$)	Treatment Groups				P
		Ipratropium Only ($n = 94$ [38.8%])	Magnesium Only ($n = 13$ [5.4%])	Magnesium and Ipratropium ($n = 42$ [17.4%])	No Adjunct ($n = 93$ [38.4%])	
Location, *n* (%)						
Akron	19 (7.9)	10 (52.6)	0 (0)	7 (36.8)	2 (10.5)	<.001
Cincinnati	101 (41.7)	6 (5.9)	10 (9.9)	2 (2)	83 (82.2)	
Cleveland	58 (24)	48 (82.8)	1 (1.7)	8 (13.8)	1 (1.7)	
Columbus	52 (21.5)	25 (48.1)	1 (1.9)	25 (48.1)	1 (1.9)	
Dayton	6 (2.5)	5 (83.3)	0 (0)	0 (0)	1 (16.7)	
Toledo	6 (2.5)	0 (0)	1 (16.7)	0 (0)	5 (83.3)	
Sex, *n* (%)						
Male	146 (60.3)	56 (38.4)	8 (5.5)	26 (17.8)	56 (38.4)	.995
Female	96 (39.7)	38 (39.6)	5 (5.2)	16 (16.7)	37 (38.5)	
Age, y, median (IQR)	6.5 (4.0–10.4)	5.7 (4.0–9.6)[a]	8.0 (3.2–12.5)	8.0 (6.0–12.0)[b]	5.7 (3.3–9.3)[a]	
Weight, kg, median (IQR)	23.7 (16.5–37.4)	21.8 (16.4–34.1)[a]	37.2 (14.5–38.5)	31.9 (23.4–49.1)[b]	20.7 (15.5–32.0)[a]	
Race and/or ethnicity, *n* (%)						
African American	119 (49.2)	54 (45.4)	6 (5)	19 (16)	40 (33.6)	.699
White	60 (24.8)	18 (30)	5 (8.3)	11 (18.3)	26 (43.3)	
Hispanic	7 (2.9)	3 (42.9)	0 (0)	1 (14.3)	3 (42.9)	
Unknown race	56 (23.1)	19 (33.9)	2 (3.6)	11 (19.6)	24 (42.9)	
Gestational age, *n* (%)						
≥37 wk	140 (57.9)	54 (38.6)	8 (5.7)	25 (17.9)	53 (37.9)	.271
32–36 wk	45 (18.6)	20 (44.4)	0 (0)	10 (22.2)	15 (33.3)	
<32 wk	9 (3.7)	15 (31.3)	5 (10.4)	5 (10.4)	23 (47.9)	
Unknown	48 (19.8)	5 (55.6)	0 (0)	2 (22.2)	2 (22.2)	
Location, *n* (%)						
Ward	30 (12.4)	1 (3.3)	1 (3.3)	2 (6.7)	26 (86.7)	<.001
PICU	212 (87.6)	93 (43.9)	12 (5.7)	40 (18.9)	67 (31.6)	
Respiratory failure, *n* (%)						
Yes	45 (18.6)	18 (40)	2 (4.4)	20 (44.4)	5 (11.1)	<.001
No	197 (81.4)	76 (38.6)	11 (5.6)	22 (11.2)	88 (44.7)	

For age and weight, each treatment group was compared individually with each other treatment group in post hoc, pairwise testing. For both age and weight, ipratropium only differed significantly from dual therapy, and dual therapy differed significantly from no adjunct; no other pairwise comparisons were statistically significant. —, not applicable.

[a] $P < .05$ versus dual therapy (magnesium and ipratropium) for age and weight by Kruskal-Wallis ANOVA with Dunn's test.

[b] $P < .05$ versus no adjunctive therapy for age and weight by Kruskal-Wallis ANOVA with Dunn's test.

demographics, treatment center, and respiratory failure as a marker of severity of illness did not change these associations. Both drugs were used commonly but not universally in this cohort of children with severe asthma exacerbations, suggesting that there is communal equipoise for interventional trials.

In this observational study, magnesium was associated with unfavorable findings in all 3 assessed outcomes, whereas ipratropium was not associated with longer duration of continuous albuterol or longer hospital LOS. The associations between magnesium usage and unfavorable outcomes likely reflect preferential administration to children with more severe symptoms that we were unable to adjust for in this secondary analysis, but other mechanisms may explain this finding. It is possible that magnesium worsens pulmonary mechanics, perhaps by depressing consciousness and promoting atelectasis, but this is unlikely given several trials in which pulmonary function testing in pediatric emergency department patients was improved by magnesium, including 1 randomized study in which magnesium therapy was more efficacious than terbutaline or aminophylline.[15,20–22] It is also possible that clinicians decided to wean albuterol more slowly in patients given magnesium. A prospective interventional study is needed to establish if magnesium causes any change in outcomes of children treated with continuous albuterol.

Ipratropium may also be preferentially administered to patients with more severe cases. If that were the case, one would expect to find associations between

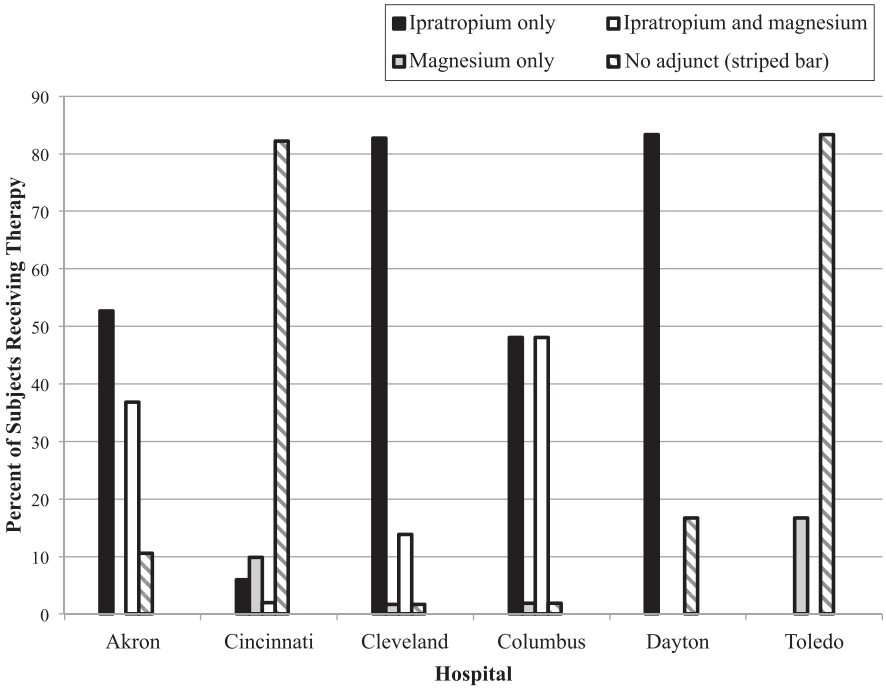

FIGURE 2 Percentage of subjects at each institution who were in each treatment group. Medication use varied significantly between centers ($P < .001$ by χ^2).

ipratropium usage and unfavorable outcomes, but we did not find such associations. Ipratropium may actually have been efficacious in these sicker patients, as shown by the lack of an association with longer duration of continuous albuterol or hospital LOS. However, the association between ipratropium use and longer time to q4 albuterol does not support efficacy. In addition, ipratropium usage by center was close to an all-or-none phenomenon, suggesting that its use is heavily influenced by local practice and not patient-specific factors like illness severity. Generally, children either received ipratropium because they were patients in Akron, Cleveland, Columbus, or Dayton, or they did not receive it because they were in Cincinnati or Toledo. Therefore, it is not surprising that there was no association between ipratropium use and either duration of continuous albuterol or hospital LOS. The association between ipratropium use and longer time to q4 albuterol may reflect differences in albuterol weaning rates in the care paths at these 2 groups of hospitals. Again, only a prospective study can truly test if ipratropium is associated with improved outcomes in this patient population.

Usage of both magnesium and ipratropium was somewhat lower in our cohort than in previous reports of PICU patients with asthma. In our cohort, 56.2% of children received ipratropium. This is somewhat lower than the ~70% usage seen in data from the Pediatric Health Information System database, but it is similar to the 59% usage among the CPCCRN centers.[11] Magnesium was administered in 22.7% of our subjects compared with the ~40% usage in the Pediatric Health Information System database and CPCCRN centers.[11] Usage of both medications also varied greatly among the 6 centers contributing to our cohort. Among the 4 centers (Akron, Cincinnati, Cleveland, and Columbus) that contributed 95% of our subjects, ipratropium usage ranged from 7.9% to 96.6%, and magnesium usage ranged from 11.9% to 50.0%. Although there are likely some patient-specific factors that influence this heterogeneity, a need for interventional trials is supported by these wide variations in care support. Prospective, randomized controlled trials of these drugs could reduce variation in care regardless of the direction of their findings, either by establishing efficacy (leading to increased prescription and improved clinical outcomes) or by proving no benefit (leading to reduced prescription and lower costs).

Continuous albuterol has traditionally been limited to the ICU setting, and nearly 90% of our subjects were initially admitted to their center's PICU.[23] PICU care was associated with shorter times until q4 albuterol and hospital discharge in our models, which supports this practice, although it may reflect center-related differences in practice. However, some centers are reporting increased usage of continuous albuterol in the general pediatric wards.[23] In our study, a substantial number (18.6%) of children were treated with respiratory

TABLE 2 Outcomes for All Subjects and for Each Treatment Group

Outcome	Duration for All Subjects ($N = 242$)	Treatment Group			
		Ipratropium Only ($n = 94$)	Magnesium Only ($n = 13$)	Magnesium and Ipratropium ($n = 42$)	No Adjunct ($n = 93$)
Duration of continuous albuterol, h, median (IQR)	7.0 (2.8–12.0)	4.9 (2.0–10.0)[a]	7.5 (2.5–16.0)	11.0 (5.6–28.6)[b]	7.0 (3.5–10.4)[a]
Time to q4 albuterol, h, mean (IQR)	38.7 (24.9–64.6)	44.3 (29.5–64.6)[a,b]	50.7 (28.8–67.3)[b]	71.3 (46.9–99.3)[b]	26.7 (19.7–38.3)[a]
Hospital LOS, h, mean (IQR)	49.0 (32.0–77.7)	57.7 (41.1–79.1)[a,b]	57.0 (42.3–83.8)[b]	77.3 (50.8–104.4)[b]	33.7 (26.8–45.2)[a]

[a] $P < .05$ versus dual therapy (magnesium and ipratropium) by Kruskal-Wallis ANOVA with Dunn's test.
[b] $P < .05$ versus no adjunctive therapy by Kruskal-Wallis ANOVA with Dunn's test.

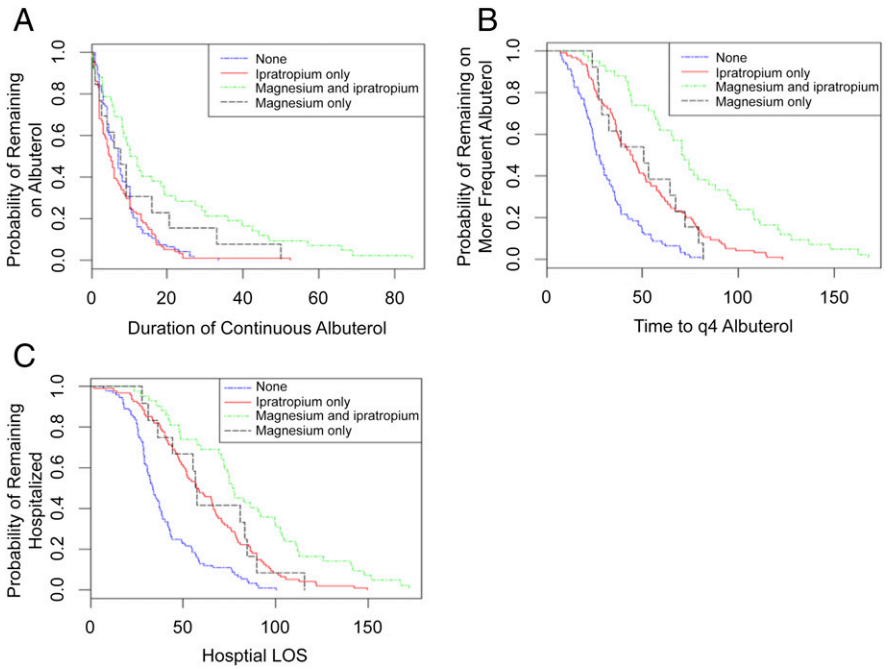

FIGURE 3 Kaplan-Meier plots of the duration of continuous albuterol, time until q4 albuterol, and hospital LOS for each of the 4 treatment groups. A, Duration of continuous albuterol. B, Time until q4 albuterol. C, Hospital LOS. Shorter "survival" times represent shorter durations of treatment.

support, including HFNC, NIPPV, or IMV. Clinicians should balance the possible need for these additional respiratory support modalities with considerations of cost and efficiency when designing inpatient asthma care algorithms that direct where in their hospital network children requiring continuous albuterol should be treated.

A major strength of our study was the ability to study children who were prospectively enrolled as part of the OPAR study, a statewide consortium of the 6 major children's hospitals in Ohio. However, there were also important limitations. Our analyses could only adjust for variables that were available as part of the OPAR. Specific medication administration timing data were unavailable, so it is impossible to assess if adjunctive therapies were administered to subjects who had already required prolonged courses of continuous albuterol in an effort to decrease albuterol use. We did adjust for the use of additional respiratory support (HFNC, NIPPV, or IMV) as a marker of illness severity, but other measures of illness severity such as a uniform asthma severity score, dyspnea scores, vital signs, controller medication use, and clinical examination findings were not available. The associations between magnesium use and unfavorable outcomes may have become insignificant if such variables were available and adjusted for because it is possible that patients who received magnesium were sicker than patients who did not. This is supported by the fact that children receiving no adjunct therapy had the shortest times until q4 albuterol and hospital discharge. Our findings should therefore be viewed primarily as hypothesis generating and not as sufficient evidence to influence care decisions. We also stratified our analysis by treatment center, but differences between each center's unique asthma care path may still have influenced our findings. Typical care at all centers for children on continuous albuterol includes serial assessments to evaluate if therapy can be de-escalated, including use of a standardized assessment (eg, hourly scoring using the Pediatric Asthma Severity Score) at 5 centers. We also lacked data on medication dosages and adverse events that may be related to the use of these therapies. Despite these limitations, these data represent the most comprehensive report of ipratropium and magnesium use in children with severe asthma hospitalizations to date. Please note, neither ipratropium nor magnesium are specifically approved by the Food and Drug Administration for the treatment of status asthmaticus in children.

TABLE 3 Factors Associated With Outcomes in Adjusted Cox Proportional Hazards Models

Variable	Duration of Continuous Albuterol		Time to q4 Albuterol		Hospital LOS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Magnesium use	0.54 (0.37–0.77)	<.001	0.38 (0.26–0.55)	<.001	0.41 (0.28–0.60)	<.001
Ipratropium use	0.97 (0.58–1.62)	.896	0.56 (0.33–0.94)	.027	0.78 (0.47–1.30)	.340
Female	0.81 (0.61–1.07)	.141	0.92 (0.69–1.24)	.597	1.01 (0.75–1.35)	.941
African American	0.6 (0.27–1.31)	.201	0.86 (0.39–1.86)	.694	0.78 (0.35–1.70)	.525
White	0.49 (0.22–1.12)	.091	0.7 (0.31–1.59)	.393	0.54 (0.23–1.25)	.149
Unknown race	0.56 (0.25–1.27)	.164	0.78 (0.34–1.79)	.565	0.75 (0.33–1.72)	.502
Location: PICU	0.87 (0.56–1.35)	.543	1.64 (1.05–2.55)	.028	1.65 (1.06–2.58)	.026
Respiratory failure	0.86 (0.52–1.42)	.557	0.54 (0.33–0.90)	.017	0.67 (0.40–1.12)	.129

HRs <1 signify longer time until intermittent albuterol, longer time until q4 albuterol, and longer time until hospital discharge, respectively. These analyses were adjusted for sex, race and/or ethnicity, treatment location, and respiratory failure.

CONCLUSIONS

Ipratropium and magnesium are both often used in children with severe asthma hospitalizations requiring continuous albuterol therapy. Magnesium use was associated with unfavorable outcomes, but this may reflect the inability to adequately adjust for preferential administration to patients with more severe cases in this secondary analysis. Ipratropium use was

not consistently associated with unfavorable outcomes, but prescription was nearly universal at some centers and extremely rare at others, limiting the interpretation of those findings. Given the high prevalence of asthma in contemporary PICUs, the wide variations in practice, and the potential to improve outcomes and hospital costs, prospective trials of adjunctive therapies in critical asthma are needed.

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