Fatal and Near-Fatal Asthma in Children: The Critical Care Perspective

Christopher J. L. Newth, MD, FRCPC[1], Kathleen L. Meert, MD[2], Amy E. Clark, MS[3], Frank W. Moler, MD[4], Athena F. Zuppa, MD[5], Robert A. Berg, MD[5], Murray M. Pollack, MD[6], Katherine A. Sward, PhD, RN[7], John T. Berger, MD[8], David L. Wessel, MD[8], Rick E. Harrison, MD[9], Jean Reardon, BSN, RN[8], Joseph A. Carcillo, MD[10], Thomas P. Shanley, MD[4], Richard Holubkov, PhD[3], J. Michael Dean, MD[3], Allan Doctor, MD[11], and Carol E. Nicholson, MD[12], for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network*

Objective To characterize the clinical course, therapies, and outcomes of children with fatal and near-fatal asthma admitted to pediatric intensive care units (PICUs).

Study design This was a retrospective chart abstraction across the 8 tertiary care PICUs of the Collaborative Pediatric Critical Care Research Network (CPCCRN). Inclusion criteria were children (aged 1-18 years) admitted between 2005 and 2009 (inclusive) for asthma who received ventilation (near-fatal) or died (fatal). Data collected included medications, ventilator strategies, concomitant therapies, demographic information, and risk variables.

Results Of the 261 eligible children, 33 (13%) had no previous history of asthma, 218 (84%) survived with no known complications, and 32 (12%) had complications. Eleven (4%) died, 10 of whom had experienced cardiac arrest before admission. Patients intubated outside the PICU had a shorter duration of ventilation (median, 25 hours vs 84 hours; $P < .001$). African-Americans were disproportionately represented among the intubated children and had a shorter duration of intubation. Barotrauma occurred in 15 children (6%) before admission. Pharmacologic therapy was highly variable, with similar outcomes.

Conclusion Of the children ventilated in the CPCCRN PICUs, 96% survived to hospital discharge. Most of the children who died experienced cardiac arrest before admission. Intubation outside the PICU was correlated with shorter duration of ventilation. Complications of barotrauma and neuromyopathy were uncommon. Practice patterns varied widely among the CPCCRN sites. *(J Pediatr 2012; ■: ■-■).*

See editorial, p •••

The Centers for Disease Control and Prevention reports a high and increasing prevalence of asthma among US children, with a rise from 5.8% in 2003 to 9.6% in 2007. Asthma currently affects more than 7 million American children,[1] with status asthmaticus the most common medical emergency.[2] The National Institutes of Health (NIH) has developed classification and therapy guidelines to address this major public health problem.[3] Interestingly, there is a paucity of published data on mechanically ventilated children critically ill with status asthmaticus. The NIH guidelines do not address the relatively few children with sufficiently severe asthma to reach the pediatric intensive care unit (PICU). Surveys of asthma management practices in PICUs have demonstrated wide variability, including inconsistent patterns of therapy sequencing and escalation.[4-6] Thus, it is difficult to define best practices, develop guidelines, or launch scientific efforts to investigate key questions that might inform clinical management.

Previous investigators have recommended the value of descriptive data in asthmatic children with fatal and near-fatal events.[7] In this spirit, the Collaborative Pediatric Critical Care Research Network (CPCCRN) investigators

CPCCRN	Collaborative Pediatric Critical Care Research Network
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
IV	Intravenous
LMV	Length of mechanical ventilation
NIH	National Institutes of Health
PICU	Pediatric intensive care unit

From the [1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA; [2]Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI; [3]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT; [4]Department of Pediatrics, University of Michigan, Ann Arbor, MI; [5]Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; [6]Department of Pediatrics, Phoenix Children's Hospital, Phoenix, AZ; [7]College of Nursing and Department of Biomedical Informatics, University of Utah, Salt Lake City, UT; [8]Department of Pediatrics, Children's National Medical Center, Washington, DC; [9]Department of Pediatrics, University of California at Los Angeles, Los Angeles, CA; [10]Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA; [11]Department of Pediatrics, Washington University School of Medicine; and [12]*Eunice Kennedy Shriver* National Institute of Child Health and Development, Bethesda, MD

*A list of members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network is available at www.jpeds.com (**Appendix**).

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conducted an initial, retrospective study of PICU patients with asthma. Our purpose was to identify the major areas of variability in drug treatment and ventilatory assistance strategies with the aim of informing later prospective studies, and to ascertain appropriate outcome measures for future trials in critical asthma. Specifically, we sought to characterize the course and therapies used to manage children with near-fatal asthma (ie, those who received mechanical ventilation and survived) or fatal asthma who were admitted to a CPCCRN PICU.

Methods

A retrospective study was conducted across the 8 children's hospitals of the CPCCRN. Patients aged 1-18 years with a primary admitting diagnosis of acute exacerbation of asthma or status asthmaticus who were deemed ill enough to require admission to the PICU of any CPCCRN hospital for ongoing therapy were defined as having critical asthma. (We acknowledge that our definition of critical asthma is not universally accepted. The term "critical asthma" has been earlier used in clinical practice guidelines in pediatrics,[8] where it meant severe asthma in the Emergency Department [ED] and did not refer to admission to the PICU.)

All children with critical asthma admitted between January 1, 2005, and December 31, 2009, who received endotracheal intubation and ventilation (near-fatal asthma) or who died (fatal asthma) in a CPCCRN hospital were included in the study. Patients with cystic fibrosis or bronchiolitis were excluded. If a patient was admitted to the hospital more than once during the study period, then each hospitalization for critical asthma during which the patient was intubated and ventilated was included. If a patient was admitted to the PICU more than once during the same hospitalization, then only the first PICU admission in which the patient was intubated and ventilated was included. Potential cases were identified from PICU logs and hospital databases and then screened by the site's principal investigator to determine study eligibility. Each site's Institutional Review Board approved the study and granted a waiver of informed consent.

The Data Coordinating Center at the University of Utah trained researchers at each site to review records and collect data. Data were entered into a secure, encrypted Internet site. The Data Coordinating Center staff provided ongoing data review and contacted researchers at the sites to resolve data queries.

Data collected included (1) demographic data, including age, sex, race/ethnicity, height, weight, and primary payer type; (2) asthma history, including timing of diagnosis, previous hospital or PICU admissions for asthma, allergies, eczema, psychiatric or behavioral disorders, substance abuse, family history of asthma, chronic asthma medications within 30 days before admission, other medical conditions, and noncompliance with asthma therapy; (3) admission data, including hospital and PICU admission and discharge dates, source of admission, mental status, pulse oximetry data, vital signs, and presence of cardiac arrest or barotrauma before admission; (4) ventilation data, including blood gas analyses before intubation and extubation, intubation and extubation dates and times, and initial and final ventilator settings in the PICU; (5) use of inhalational anesthesia; (6) use of extracorporeal membrane oxygenation (ECMO); (7) pharmacologic therapies used before intubation at a referring or CPCCRN hospital and during and after ventilation; and (8) outcomes, including complications (barotrauma, neuromyopathy, and central nervous system deficits), mortality, and mode and cause of death. Mode of death was specified as withdrawal of support, cessation of neurologic function, or failed cardiopulmonary resuscitation. Data on asthma scores were not requested, because none of our sites use these scores.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and clinical variables overall and across the study sites. Categorical data are presented as absolute counts and percentages. Continuous data are presented as means and SDs if normally distributed and as medians and IQRs if the distributions are skewed. With the exception of pharmacologic therapies for which "no" and "not documented" were combined, unavailable (missing) values were excluded from calculations of percentages and summary statistics. In survivors only, univariate associations between key baseline and early clinical factors with length of mechanical ventilation (LMV), classified as either <72 or ≥ 72 hours, were evaluated. Statistical testing was based on the χ^2 or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Statistical significance was defined as $P < .05$, and all analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, North Carolina).

Results

A total of 261 patients with near-fatal and fatal asthma were identified across the CPCCRN sites during the 5-year study period, of whom 260 (99.6%) were intubated and ventilated. One patient was not intubated and died, and 10 (4%) of the intubated patients died. All fatal cases had been admitted to the PICU before death. Case demographic data by study site are presented in Table I (available at www.jpeds.com). Comparing our asthma cohort with overall CPCCRN admissions during the study period shows that African-American children were overrepresented (62% vs 23%; $P < .0001$) and Hispanic children were underrepresented (10% vs 19%; $P = .0008$).

A previous diagnosis of asthma was documented in 226 patients (87%), and 33 patients (13%) were newly diagnosed during the index hospitalization. Among the previously diagnosed patients, 132 (63%) had no previous hospital admissions for asthma in the year preceding the index admission, 43 (21%) had 1 previous admission, 20 (10%) had 2 admissions, and 13 (6%) had 3 or more admissions. Regarding previous PICU admissions for asthma in the year preceding the index admission, 182 (86%) had none, 21 (10%) had 1, 7 (3%) had 2, and 1 (0.5%) had 3. Among all patients,

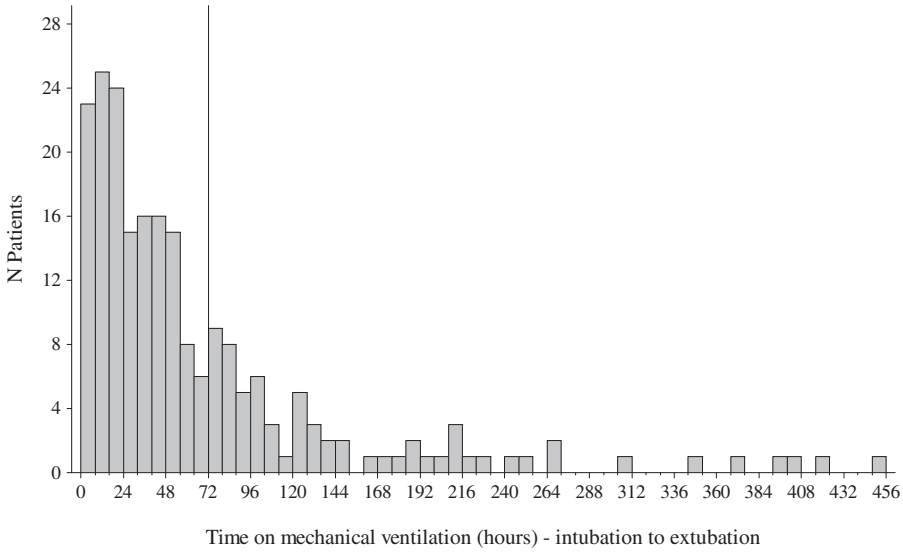

Figure 2. Number of patients versus LMV (in hours) for the 260 eligible patients in the study cohort. One observation (a patient with an LMV of >800 hours) is omitted. The *vertical line* represents the cutoff dividing the patients with an LMV of <72 hours from those with an LMV of >72 hours.

76 (29%) had a documented nonfood allergy and 51 (20%) had a food allergy. Allergic exposure precipitated the admission in 19 of 102 patients (19%) with known allergies. Medical history findings included eczema in 40 patients (15%), psychiatric or behavioral disorders in 13 (5%), substance abuse in 4 (2%), other medical conditions in 132 (51%), and documented family history of asthma in 151 (58%). Asthma medications used within 30 days before admission included short-acting inhaled β-agonists in 236 (91%), long-acting inhaled β-agonists in 37 (14%), inhaled corticosteroids in 129 (50%), oral corticosteroids in 55 (21%), leukotriene-receptor antagonists in 64 (25%), inhaled anticholinergics in 15 (6%), antihistamines in 9 (4%), methylxanthines in 1 (0.4%), and home supplemental oxygen in 6 (2%). Forty-eight patients (18%) were reported as noncompliant with chronic asthma medications.

Admission data showed that 141 patients (54%) were transferred to the PICU from an outside ED, 86 (33%) were transferred from the study site ED, 17 (7%) were transferred from a site hospital ward, 13 (5%) were admitted directly to the PICU at the time of hospital admission from a physician's office or clinic, and 4 (2%) were admitted from an outside PICU. The mental status of patients not intubated before PICU admission (n = 81) was reported as alert in 74 patients (91%), obtunded in 3 patients (4%), pharmacologically sedated in 3 patients (4%), and unknown in 1 patient (1%). Fifteen patients (6%) had experienced pulmonary barotrauma before PICU admission, including 10 with pneumomediastinum, 6 with subcutaneous emphysema, and 4 with pneumothorax. Twenty-five children (10%) had a cardiac arrest before PICU admission (16 African Americans; 64%; P = not significant), of whom 15 survived, 5 with central nervous system deficits including one with neuromyopathy and one with residual barotrauma. Ten children died. **Figure 1** (available at www.jpeds.com) shows blood gas PCO_2 values before intubation (measured in only 48% of patients) and, for survivors, LMV, and PICU and hospital length of stay by site. **Figure 2** shows the overall distribution of LMV.

Of the 259 patients with documented timing of intubation, 178 (69%) were intubated outside of a CPCCRN PICU. These other locations included the referring hospital (125; 70%), study site ED (36; 20%), during transport (13; 7%), operating room (2; 1%), hospital ward (1; 1%), and 1 (1%) unknown. Pressure control was the most frequent initial mode of conventional ventilation (63%). High-frequency oscillatory ventilation was used in 9 patients (3%). Mechanical ventilation and blood gas data are shown in **Table II**. Helium–oxygen gas mixtures were administered before intubation in only 5% of children intubated children before admission to the PICU, compared with 30% of those intubated in the PICU.

Noninvasive positive-pressure ventilation was administered to 42 patients (16%) before intubation and in 28 (11%) after extubation (**Table II**). Inhalational anesthesia (isoflurane) was used in 8 patients (3%) (median duration, 74 hours; IQR, 52-107 hours). ECMO was used in 3 patients (median duration, 139 hours; IQR, 116-141 hours). Seventeen patients (7%) underwent bronchoscopy during ventilation, and 2 (1%) did so after extubation. Neuromuscular blockade at any time during ventilation (after endotracheal intubation) was provided to 170 patients (65%), with its use varying widely by site (33%-100%).

Associations of demographic and early clinical factors with LMV is shown in **Table III**. Among the 216 patients who

Table II. Mechanical ventilation and blood gas data (n = 260)

	Number	n (%)
Noninvasive ventilation before intubation	254	42 (17)
Initial ventilator mode in PICU	257	
Pressure control		162 (63)
Volume control		44 (17)
Pressure-regulated volume control		36 (14)
Pressure support with PEEP		15 (6)
Final ventilator mode*	248	
Pressure control		84 (34)
Volume control		50 (20)
Pressure-regulated volume control		25 (10)
Pressure support with PEEP		89 (36)
Noninvasive ventilation immediately postextubation*	250	16 (6)
Noninvasive ventilation any time postextubation*	250	28 (11)
		Median (IQR)
Blood gas values before intubation		
pH	126	7.26 (7.17-7.35)
PCO_2, torr†	126	52 (38-68)
PaO_2, torr‡	49	109 (65-166)
Initial ventilator settings in PICU		
Inspired O_2, %	256	70 (40-100)
Rate, breaths/minute§	240	16 (12-20)
Peak inspiratory pressure, cm H_2O¶	161	30 (25-36)
Tidal volume, mL/kg‖	77	8 (7-9)
Inspiratory time, seconds¶	150	0.9 (0.8-1.0)
PEEP, cm H_2O	255	5 (5-6)
Blood gas values before extubation*		
pH	236	7.41 (7.36-7.45)
PCO_2, torr†	236	41 (36-46)
PaO_2, torr‡	156	91 (73-110)
Final ventilator settings*		
Inspired O_2, %	248	40 (30-40)
PEEP, cm H_2O	247	5 (5-5)
LMV, hours*	216	42 (18-84)
Length of noninvasive mechanical ventilation postextubation, hours	28	27 (17-70)

PEEP, positive end-expiratory pressure.
*Survivors only.
†Includes arterial, capillary, and corrected venous PCO_2; correction is venous PCO_2 − 6 torr.
‡Includes arterial PO_2 only.
§Includes cases of pressure control, volume control, and pressure-regulated volume control only.
¶Includes cases of pressure control only.
‖Includes cases of volume control and pressure-regulated volume control only.

survived to hospital discharge for whom complete ventilation data were available, 148 (69%) had an LMV of <72 hours and 68 (31%) had an LMV of ≥72 hours. Children intubated outside the CPCCRN PICUs (80% of whom were African-American) had considerably shorter LMV and duration of PICU stays compared with those intubated in the PICUs (median LMV, 25 hours vs 84 hours, $P < .001$; median PICU stay, 56 hours vs 137 hours; $P < .001$). These results do not appear to be affected by overall shorter LMV at sites with a preponderance of African-American admissions.

Pharmacologic therapies administered before intubation and during and after mechanical ventilation were highly variable, as shown in Tables IV (available at www.jpeds.com), V, and VI (available at www.jpeds.com). There was wide variability in the use of intravenous (IV) β_2 agonists, with most sites favoring terbutaline over epinephrine and isoproterenol.

A total of 218 patients (84%) survived PICU admission with no known complications, 32 (12%) survived with complications and 11 (4%) died. Among survivors with complications, 11 (34%) had central nervous system deficits, 8 (25%) had barotraumas, and 4 (13%) had neuromyopathy. Five patients (2%) without barotrauma at the time of admission had residual barotrauma at the time of PICU discharge. Six nonsurvivors (55%) were moribund on arrival to the PICU. The mode of death was cessation of neurologic function in 7 (64%), withdrawal of support in 2 (18%), and failed cardiopulmonary resuscitation in 2 (18%). Documented cause of death in the chart was anoxic brain injury in 6 (55%), cardiac arrest in 2 (18%), pneumonia in 1 (9%), multiple organ failure in 1 (9%), and not documented 1 (9%). Autopsy was performed in 4 patients.

Discussion

In this study, most of the pediatric patients with asthma who received mechanical ventilation and were admitted to a CPCCRN PICU survived without short-term complications. Ten of the 11 children in our cohort who died experienced cardiac arrest before PICU admission. Geographic location of endotracheal intubation is correlated with LMV. African-American children were significantly overrepresented in our sample, and Hispanic children were underrepresented. Barotrauma during the course of mechanical ventilation for critical asthma was an uncommon event, as was neuromyopathy following therapy with steroids and neuromuscular blockade. There was wide variability in the pharmacologic treatment of critical asthma among the CPCCRN sites.

In describing contemporary pediatric critical care management for life-threatening childhood asthma, the most obvious characteristic is inconsistency of approach. The lack of standard practice is likely related to conflicting or scanty evidence-based data. The lack of national guidelines for critical asthma[3,9-12] reflects this inadequate information.

In this study, patients who were ultimately admitted to the PICU were more likely to be intubated in the referring or CPCCRN hospital ED than in the PICU itself. The median LMV was shorter in the 69% of patients intubated before PICU admission than in the 31% eventually intubated within the PICU (25 hours vs 84 hours), as reported previously.[13] This geographic variability in intubation site may reflect health care disparities, with some children receiving less preventive therapy or presenting later. It could represent overreaction by clinicians less familiar with caring for children with severe asthma, but also may be due to a perceived or real lack of time in the ED to maximize drug therapy. It is also possible that early intubation and ventilation is beneficial rather than detrimental in status asthmaticus, potentially improving drug delivery to the airways, and is safer with modern ventilation techniques. Many of these children may have acute, asphyxial asthma (type 2) with sudden, severe onset but a rapid response to therapy.[14] Thus, we can speculate that patients intubated in the PICU and with a longer LMV have

Table III. Association of demographic and early clinical factors with LMV*

	Number	LMV		*P* value
		<72 hours (n = 148)	≥72 hours (n = 68)	
Age, years, median (IQR)	216	7.5 (2.6-12.0)	5.4 (2.1-9.3)	.14
Body mass index, median (IQR)	86	17.5 (15.0-23.5)	18.1 (15.3-20.1)	.98
Sex, n (%)				.88
Male	130	90 (69)	40 (31)	
Female	86	58 (67)	28 (33)	
Race, n (%)†				<.001
African-American	123	99 (80)	24 (20)	
Caucasian	63	33 (52)	30 (48)	
Asian	6	3 (50)	3 (50)	
Other	2	1 (50)	1 (50)	
Ethnicity, n (%)†				.03
Hispanic or Latino	15	7 (47)	8 (53)	
Not Hispanic or Latino	154	115 (75)	39 (25)	
Insurance, n (%)†				.17
Commercial	87	55 (63)	32 (37)	
Medicaid	119	87 (73)	32 (27)	
Other	8	4 (50)	4 (50)	
Asthma diagnosis, n (%)†				.57
New diagnosis	30	22 (73)	8 (27)	
Previous diagnosis	185	126 (68)	59 (32)	
Known allergic exposure precipitating admission, n (%)				.48
Yes	18	11 (61)	7 (39)	
No	198	137 (69)	61 (31)	
Known cardiac arrest before admission, n (%)				.52
Yes	12	7 (58)	5 (42)	
No	204	141 (69)	63 (31)	
Barotrauma evidence before admission, n (%)†				.44
Yes	8	7 (88)	1 (13)	
No	207	140 (68)	67 (32)	
Source of admission to PICU, n (%)				<.001
Direct admission	11	4 (36)	7 (64)	
Transfer from outside ED/ICU	107	85 (79)	22 (21)	
Admit through study ED	83	52 (63)	31 (37)	
Transfer from floor	15	7 (47)	8 (53)	
Intubated before CPCCRN PICU, n (%)				<.001
Yes	136	116 (85)	20 (15)	
No	80	32 (40)	48 (60)	

ICU, intensive care unit.
*Restricted to patients who survived to hospital discharge and had complete data for LMV.
†Data points missing.

slow-onset, respiratory failure type asthma (type 1). Furthermore, it is noteworthy that African-American children with near-fatal and fatal asthma were overrepresented with respect to the number admitted to the CPCCRN PICUs for all reasons (62% vs 23%). They were also intubated and ventilated for a shorter time (80%, <72 hours; Table III), whereas LMV for other racial groups were evenly distributed at 50% in each of the shorter and >72 hours groups. These findings were consistent across the CPCCRN sites and suggest that African-American children may be particularly prone to acute asphyxial asthma. Further investigation of this unexpected finding is warranted.

Blood gas analysis for CO_2 tension before intubation was available in only 126 of the 260 intubated patients (48%). Median values were similar across the centers (median pH, 7.26; PCO_2, 52 torr) but varied markedly within each center. These values are similar to those reported by Roberts et al[4] in 2002. Given the variable LMV (median, 42 hours; IQR, 18-84 hours), and lack of association of initial PCO_2 and LMV, CO_2 tension may not be a good indicator of severity of asthma for the observing clinician, as once believed.[3] The NIH guidelines do recommend considering intubation in children with $PaCO_2$ >42 torr, without reference.[3]

Pressure control was the most frequent initial mode of ventilation (63%), which may reflect a gradual acceptance of the proposal by Sarnaik et al[15] that this mode is safe, associated with shorter LMV in pediatric asthma, and theoretically provides for more uniform ventilation and improved distribution of inhaled drugs compared with the previously accepted volume control mode. Noninvasive ventilation was used in 23% of patients both before intubation and after extubation for the acute episode. Neither noninvasive nor invasive ventilation in the PICU seemed to cause additional air leaks. Fifteen children had evidence of barotrauma before PICU admission, and only 5 had a further air leak noted at the time of PICU discharge. ECMO was used in only 3 children (~1%), consistent with data from the Extracorporeal Life Support Organization registry, in which only 64 children received ECMO for asthma in a 21-year period (1986-2007).[16]

Table V. Pharmacologic therapies administered during mechanical ventilation by site

	Site 1 (n = 13)	Site 2 (n = 68)	Site 3 (n = 33)	Site 4 (n = 65)	Site 5 (n = 15)	Site 6 (n = 20)	Site 7 (n = 6)	Site 8 (n = 40)	All (n = 260)
Albuterol, n (%)									
Inhaled, intermittent	10 (77)	54 (79)	30 (91)	46 (71)	12 (80)	14 (70)	4 (67)	23 (58)	193 (74)
Inhaled, continuous	8 (62)	57 (84)	8 (24)	51 (78)	8 (53)	7 (35)	6 (100)	36 (90)	181 (70)
Corticosteroids, IV or oral, n (%)	13 (100)	66 (97)	32 (97)	63 (97)	15 (100)	20 (100)	6 (100)	40 (100)	255 (98)
Ipratropium, inhaled, n (%)	4 (31)	56 (82)	14 (42)	9 (14)	7 (47)	13 (65)	5 (83)	21 (53)	129 (50)
Terbutaline, n (%)									
IV	4 (31)	28 (41)	16 (48)	32 (49)	1 (7)	12 (60)	3 (50)	18 (45)	114 (44)
SC or IM	0	3 (4)	0	2 (3)	0	0	0	1 (3)	6 (2)
Inhaled	0	1 (1)	0	0	0	0	0	0	1 (0.4)
Isoproterenol, IV, n (%)	2 (15)	1 (1)	0	0	0	0	0	0	3 (1)
Epinephrine, n (%)									
IV	3 (23)	7 (10)	8 (24)	6 (9)	3 (20)	3 (15)	3 (50)	8 (20)	41 (16)
SC or IM	0	8 (12)	3 (9)	4 (6)	2 (13)	2 (10)	0	2 (5)	21 (8)
Inhaled	3 (23)	2 (3)	4 (12)	5 (8)	2 (13)	2 (10)	0	2 (5)	20 (8)
Atropine, IV, n (%)	8 (62)	4 (6)	3 (9)	3 (5)	1 (7)	0	0	1 (3)	20 (8)
Aminophylline/theophylline IV or oral, n (%)	6 (46)	11 (16)	2 (6)	2 (3)	3 (20)	1 (5)	2 (33)	16 (40)	43 (17)
Helium-oxygen, inhaled, n (%)	0	24 (35)	0	13 (20)	2 (13)	0	1 (17)	18 (45)	58 (22)
Magnesium sulfate, IV, n (%)	6 (46)	36 (53)	8 (24)	22 (34)	2 (13)	8 (40)	5 (83)	17 (43)	104 (40)
Ketamine, IV, n (%)	8 (62)	12 (18)	13 (39)	34 (52)	7 (47)	14 (70)	3 (50)	30 (75)	121 (47)
Neuromuscular blockade, IV, n (%)*	11 (85)	47 (69)	24 (73)	36 (55)	5 (33)	10 (50)	6 (100)	31 (78)	170 (65)
Mucolytics, inhaled, n (%)	0	0	0	1 (2)	5 (33)	0	1 (17)	4 (10)	11 (4)
Nitric oxide, inhaled, n (%)	0	0	6 (18)	1 (2)	1 (7)	0	1 (17)	2 (5)	11 (4)

IM, intramuscular; *SC*, subcutaneous.
*Neuromuscular blockade administered during mechanical ventilation, not for intubation.

The rate of IV β_2 agonist use during mechanical ventilation ranged from 27% to 75% across the CPCCRN sites. NIH guidelines[3] note a lack of data supporting the superiority of the IV β_2 agonists over inhaled β_2 agonists,[17] and specific caution is recommended for IV isoproterenol, which was used at 2 CPCCRN sites. The NIH guidelines do not address critical asthma, and thus it is difficult to put these recommendations into proper context, given that other national guidelines advocate the use of IV β_2 agonists if there is no response to continuous inhaled albuterol.[9-11] Two studies in severely ill children with asthma supporting IV albuterol (salbutamol) have been reported.[18,19] This suggests that a trial of IV versus aerosolized β_2 agonists may be feasible and valuable in patients before ventilation as well as in patients not requiring ventilation. Little information is available on the prevalence of β_2 agonist toxicity[20,21] by any route in children, and further investigation would be of value.

Given our current knowledge of the important role and efficacy of corticosteroids in the management of asthma, and the concordance of many published guidelines,[3,9-12] it is rewarding that 98% or 255 of our 260 patients received corticosteroid therapy during mechanical ventilation. In addition, 4 of the remaining 5 patients received steroids before or after a very short period of ventilation (<3 hours). Thus, 99% of the children were treated overall. Notably, 65% of the children received neuromuscular blocking agents while ventilated, and only 4 cases of subsequent neuromyopathy were reported.

Controversy persists regarding the use of both magnesium and theophylline to treat acute childhood asthma. A recent meta-analysis for magnesium found it to be effective in preventing hospitalization and in improving short-term clinical symptom scores and pulmonary function tests.[22] Its use is recommended in some published guidelines,[3,9,10] but not in others.[11] Nonetheless, although magnesium therapy in children with critical asthma has not been studied, in this investigation IV magnesium was administered to 45% of the children before intubation, to 40% during mechanical ventilation, and to 6% after extubation. In contrast, aminophylline was administered to only 4% of the children before intubation, to 17% during mechanical ventilation, and to 5% after extubation. Aminophylline has been reported to improve several important outcomes in children hospitalized with asthma (though not necessarily critical asthma) in both randomized controlled trials[23-26] and a Cochrane meta-analysis.[27] The reasons for this disparity in acceptance are unclear.

Most published guidelines recommend ipratropium bromide for severe asthma. Conflicting evidence casts doubt on its efficacy compared with modern selective β agonists.[18,28] Nonetheless, ipratropium bromide was used in only 36% of our patients before intubation and in 50% during mechanical ventilation, although use varied widely among the study sites (14%-83%). Overall, its use during ventilation in the CPCCRN PICUs was lower than the rate reported from Pediatric Health Information System data in 2005.[5]

The use of inhaled helium-oxygen gas mixtures (heliox) has theoretical potential to both decrease the work of breathing and improve the delivery of inhaled drugs in obstructed airways. Bilevel positive airway pressure therapy could possibly potentiate these effects. Nonetheless, although heliox appears to be useful in models of pediatric ventilation,[29] this therapy has demonstrated conflicting results in small clinical trials.[30,31] In the present study, 99 children (38%) received heliox at some point during the course of their PICU stay, but only 22% did so while

ventilated, similar to the 18% reported by Bratton et al[5] for an equivalent group of patients in 2005. The role of heliox with or without bilevel positive airway pressure therapy remains to be determined.

There have been several reports of death from asthma in children over the past 2 decades,[32-35] but only a few analyses of PICU management and deaths, all from single centers.[36-38] Between 1982 and 1988 in Toronto, 89 children were admitted to PICUs for status asthmaticus,[36] one-third of whom were receiving mechanical ventilation. Three children (3.4%) died from hypoxic-ischemic encephalopathy after out-of-hospital cardiac arrest.[36] A subsequent 3-year review of 19 children receiving mechanical ventilation (mean LMV, 42 hours compared with our mean of 73 hours; median, 42.6 hours) found that 11 (58%) were intubated before PICU admission, 14 (74%) were extubated within 72 hours, and none died.[37] In a study in Melbourne, Australia, over a 6-year period (1982-1988), 27 children (10%) required mechanical ventilation and 5 (18.5%) died, 4 of whom had experienced cardiac arrest before intubation.[38] The mortality rate of 4.3% in the present study is similar to that reported in the Toronto study more than 20 years ago.[36]

Recently, Melbourne investigators interviewed 410 of the 684 patients admitted to their PICU with asthma over a 15-year period (mean follow-up, 10.3 years). Asthma persisted in 88%, and 5% of the children who received mechanical ventilation during their index admission died within 10 years of discharge.[39] These data suggest that children who receive mechanical ventilation for asthma are a high-risk group and should be studied prospectively, with a view to evaluating longer-term outcomes.

Two clinical subsets of adults who die from status asthmaticus have been defined.[40,41] Type 1 (slow-onset) patients have poorly controlled, severe asthma with higher mortality. Bronchial mucus plugging is a prominent pathological finding.[42] Type 2 (fast-onset) patients have little or no history of asthma and experience fulminant bronchospasm.[41] Pathological examination shows airways without mucus plugging.[43] These subsets may not exist in children, although type 2 has been alluded to,[14] and clinical experience seems to support the existence of this subset. The possibility that these subsets exist in children as well as in adults warrants further investigation. Autopsy data were available for only 4 of our 11 patients who died. All 4 patients exhibited characteristic chronic pulmonary changes of asthma, but only 1 patient had significant bronchial mucus plugging.

Limited conclusions can be derived from this study. Ours is a retrospective cohort, and data from referring EDs were limited. We could not capture details of drug dosing or toxicity, or of how drugs were applied with respect to the severity of asthma. In addition, some elements have missing data, and it is possible there is some selection bias with regards to these missing data. We also included children as young as 1 year of age. Each case was adjudicated as having asthma by the principal investigator at each site. Although it is possible that some of these patients had bronchiolitis, for which a longer LMV would be expected, this proportion of patients ventilated <72 hours was the same for those under 2 years of age as for those older (68%).

The development of a critical asthma severity score to guide the intensity of PICU therapeutic interventions and responses would be useful. Although at least 19 different "asthma scores" are available,[44] none has been derived or validated on children with asthma requiring PICU admission.

In conclusion, this retrospective study of mechanically ventilated patients admitted to CPCCRN PICUs found significant variability in asthma therapies and ventilator strategies in critically ill children. Despite this marked variability, patients outcomes were similar, and most patients did well. This variability, along with the lack of sensitive tools for grading critical asthma severity and response to therapy, makes testing hypotheses challenging. All but one of the children who died experienced cardiac arrest before PICU admission. The marked overrepresentation of African-American children in this fatal/near-fatal cohort invites speculation about an alternative pathophysiology (eg, a predilection to fulminant bronchospasm) or possible health care disparities in this group of children. ■

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Reprint requests: Christopher J. L. Newth, MD, FRCPC, Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, 4650 Sunset Boulevard, Los Angeles, CA 90027. E-mail: cnewth@chla.usc.edu

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Appendix

CPCCRN members participating in this study: University of Utah (Data Coordinating Center), Salt Lake City, UT: J. Michael Dean, MD, MBA, Katherine Sward, PhD, RN, Jeri Burr, MS, RN-BC, CCRC, Amy Clark, MS, Richard Holubkov, PhD, Stephanie Bisping, BSN, RN, CCRP, Teresa Liu, MPH, Emily Stock, BS, Rene Enriquez, BS, Anna Davis, MPH, RN, Alecia Peterson, BS

Children's National Medical Center, Washington, DC: John Berger, MD, David Wessel, MD, Jean Reardon, BSN, RN

Children's Hospital of Pittsburgh, Pittsburgh, PA: Joseph Carcillo, MD, Michael Bell, MD, Alan C. Abraham, BA, CCRC

Children's Hospital of Michigan, Detroit, MI: Kathleen L. Meert, MD, Sabrina Heidemann, MD, Ann Pawluszka, BSN, RN

Phoenix Children's Hospital, Phoenix, AZ: Murray Pollack, MD, Heidi Dalton, MD, Christian Lawson, MS, RN

Children's Hospital of Philadelphia, Philadelphia, PA: Robert Berg, MD, Athena Zuppa, MD, Mary Ann DiLiberto, BS, RN, CCRC

Department of Pediatrics, C.S. Mott Children's Hospital at University of Michigan, Ann Arbor, MI: Tom Shanley, MD, Frank Moler, MD, Monica S. Weber, RN, BSN, CCRP

Children's Hospital Los Angeles, Los Angeles, CA: Christopher J.L. Newth, MD, FRCPC, J. Francisco Fajardo, CLS (ASCP), RN, MD, Jennifer Kwok, BS, Jonathan Serrano, BA

Mattel Children's Hospital at University of California Los Angeles, Los Angeles, CA: Mary Ann Nyc BS, MPH, Rick Harrison, MD

Washington University, St. Louis, MO: Allan Doctor, MD

National Institute of Child Health and Human Development, Bethesda, MD: Carol Nicholson, MD, Tammara Jenkins, MSN, RN.

Table I. Demographic data of cases by site

	Site 1 (n = 13)	Site 2 (n = 68)	Site 3 (n = 33)	Site 4 (n = 65)	Site 5 (n = 15)	Site 6 (n = 21)	Site 7 (n = 6)	Site 8 (n = 40)	All (n = 261)
Age, years, median (IQR)	3.7 (1.5-9.2)	10.3 (4.2-12.7)	6.5 (2.8-9.8)	6.7 (3.7-11.4)	4.0 (2.2-11.6)	8.3 (3.6-13.0)	7.7 (1.8-11.3)	5.0 (1.9-10.8)	6.8 (2.5-11.8)
Body mass index, kg/m^2, median (IQR)	18.9 (16.3-32.5)	19.8 (15.0-21.9)	15.9 (13.4-18.4)	17.6 (14.9-24.7)	16.3 (13.4-18.0)	17.3 (16.4-18.1)	18.6 (16.8-19.1)	18.6 (15.9-23.5)	18.1 (15.1-22.7)
Sex, male, n (%)	7 (54)	48 (71)	25 (76)	37 (57)	8 (53)	12 (57)	5 (83)	19 (48)	161 (62)
Race, n (%)*									
African-American	4 (57)	57 (86)	12 (50)	43 (72)	2 (15)	7 (35)	2 (50)	14 (40)	141 (62)
Caucasian	2 (29)	9 (14)	11 (46)	14 (23)	9 (69)	9 (45)	1 (25)	21 (60)	76 (33)
Asian	1 (14)	0	1 (4)	3 (5)	1 (8)	1 (5)	1 (25)	0	8 (3)
Other	0	0	0	0	1 (8)	3 (15)	0	0	4 (2)
Ethnicity, n (%)									
Hispanic	6 (46)	0	1 (3)	8 (12)	1 (7)	4 (19)	0	0	20 (8)
Non-Hispanic	7 (54)	66 (97)	22 (67)	51 (78)	13 (87)	17 (81)	4 (67)	4 (10)	184 (70)
Unknown	0	2 (3)	10 (30)	6 (9)	1 (7)	0	2 (33)	36 (90)	57 (22)
Insurance, n (%)*									
Commercial	1 (8)	17 (25)	17 (52)	29 (46)	6 (43)	14 (67)	4 (67)	17 (45)	105 (41)
Medicaid	12 (92)	51 (75)	14 (42)	31 (49)	5 (36)	5 (24)	1 (17)	19 (50)	138 (54)
Other	0	0	2 (6)	3 (5)	3 (21)	2 (10)	1 (17)	2 (5)	13 (5)

*Data points missing.

Table IV. Pharmacologic therapies administered before intubation by site

	Site 1 (n = 13)	Site 2 (n = 68)	Site 3 (n = 33)	Site 4 (n = 65)	Site 5 (n = 15)	Site 6 (n = 21)	Site 7 (n = 6)	Site 8 (n = 40)	All (n = 261)
Albuterol, n (%)									
Inhaled, intermittent	8 (62)	59 (87)	23 (70)	48 (74)	10 (67)	15 (71)	3 (50)	31 (78)	197 (75)
Inhaled, continuous	7 (54)	24 (35)	18 (55)	27 (42)	7 (47)	10 (48)	4 (67)	21 (53)	118 (45)
Corticosteroids, IV or oral, n (%)	9 (69)	50 (74)	22 (67)	42 (65)	11 (73)	13 (62)	4 (67)	29 (73)	180 (69)
Ipratropium, inhaled, n (%)	5 (38)	37 (54)	13 (39)	13 (20)	8 (53)	7 (33)	3 (50)	7 (18)	93 (36)
Terbutaline, n (%)									
IV	3 (23)	5 (7)	16 (48)	19 (29)	1 (7)	6 (29)	2 (33)	3 (8)	55 (21)
SC or IM	1 (8)	4 (6)	1 (3)	4 (6)	1 (7)	1 (5)	0	2 (5)	14 (5)
Inhaled	1 (8)	0	0	0	0	0	0	0	1 (0.4)
Isoproterenol, IV, n (%)	1 (8)	0	0	1 (2)	0	0	0	0	2 (1)
Epinephrine, n (%)									
IV	0	6 (9)	4 (12)	2 (3)	0	0	1 (17)	4 (10)	17 (7)
SC or IM	1 (8)	37 (54)	12 (36)	35 (54)	6 (40)	3 (14)	0	9 (23)	103 (39)
Inhaled	1 (8)	0	4 (12)	9 (14)	2 (13)	0	0	5 (13)	21 (8)
Atropine, IV, n (%)	1 (8)	7 (10)	4 (12)	11 (17)	0	2 (10)	0	3 (8)	28 (11)
Aminophyline/theophylline IV or oral, n (%)	1 (8)	1 (1)	0	1 (2)	2 (13)	1 (5)	1 (17)	4 (10)	11 (4)
Helium-oxygen, inhaled, n (%)	0	4 (6)	2 (6)	14 (22)	3 (20)	1 (5)	0	8 (20)	32 (12)
Magnesium sulfate, IV, n (%)	4 (31)	30 (44)	18 (55)	34 (52)	5 (33)	9 (43)	2 (33)	16 (40)	118 (45)
Ketamine, IV, n (%)	1 (8)	0	5 (15)	3 (5)	1 (7)	3 (14)	3 (50)	2 (5)	18 (7)

SC, subcutaneous; *IM*, intramuscular.

Table VI. Pharmacologic therapies administered after extubation by site

	Site 1 (n = 13)	Site 2 (n = 66)	Site 3 (n = 32)	Site 4 (n = 62)	Site 5 (n = 15)	Site 6 (n = 17)	Site 7 (n = 6)	Site 8 (n = 40)	All (n = 251)
Albuterol, n (%)									
Inhaled, intermittent	12 (92)	63 (95)	29 (91)	61 (98)	15 (100)	15 (88)	6 (100)	38 (95)	239 (95)
Inhaled, continuous	3 (23)	34 (52)	9 (28)	19 (31)	4 (27)	4 (24)	3 (50)	23 (58)	99 (39)
Corticosteroids, IV or oral, n (%)	8 (62)	61 (92)	32 (100)	52 (84)	10 (67)	16 (94)	5 (83)	37 (93)	221 (88)
Ipratropium, inhaled, n (%)	7 (54)	42 (64)	15 (47)	5 (8)	6 (40)	15 (88)	4 (67)	17 (43)	111 (44)
Terbutaline, n (%)									
IV	3 (23)	4 (6)	10 (31)	8 (13)	0	4 (24)	1 (17)	1 (3)	31 (12)
SC or IM	0	0	0	1 (2)	0	1 (6)	0	0	2 (1)
Inhaled	0	0	0	0	0	0	0	0	0
Isoproterenol, IV, n (%)	1 (8)	0	0	0	0	0	0	0	1 (0.4)
Epinephrine, n (%)									
IV	0	0	2 (6)	1 (2)	0	0	0	1 (3)	4 (2)
SC or IM	0	2 (3)	0	3 (5)	0	0	0	0	5 (2)
Inhaled	1 (8)	2 (3)	6 (19)	6 (10)	6 (40)	0	0	1 (3)	22 (9)
Atropine, IV, n (%)	0	0	0	0	0	0	0	0	0
Aminophyline/theophylline IV or oral, n (%)	4 (31)	3 (5)	0	0	1 (7)	1 (6)	2 (33)	2 (5)	13 (5)
Helium-oxygen, inhaled, n (%)	0	12 (18)	0	15 (24)	4 (27)	0	0	20 (50)	51 (20)
Magnesium sulfate, IV, n (%)	0	5 (8)	3 (9)	4 (6)	0	0	0	3 (8)	15 (6)
Ketamine, IV, n (%)	1 (8)	0	2 (6)	4 (6)	0	1 (6)	0	1 (3)	9 (4)

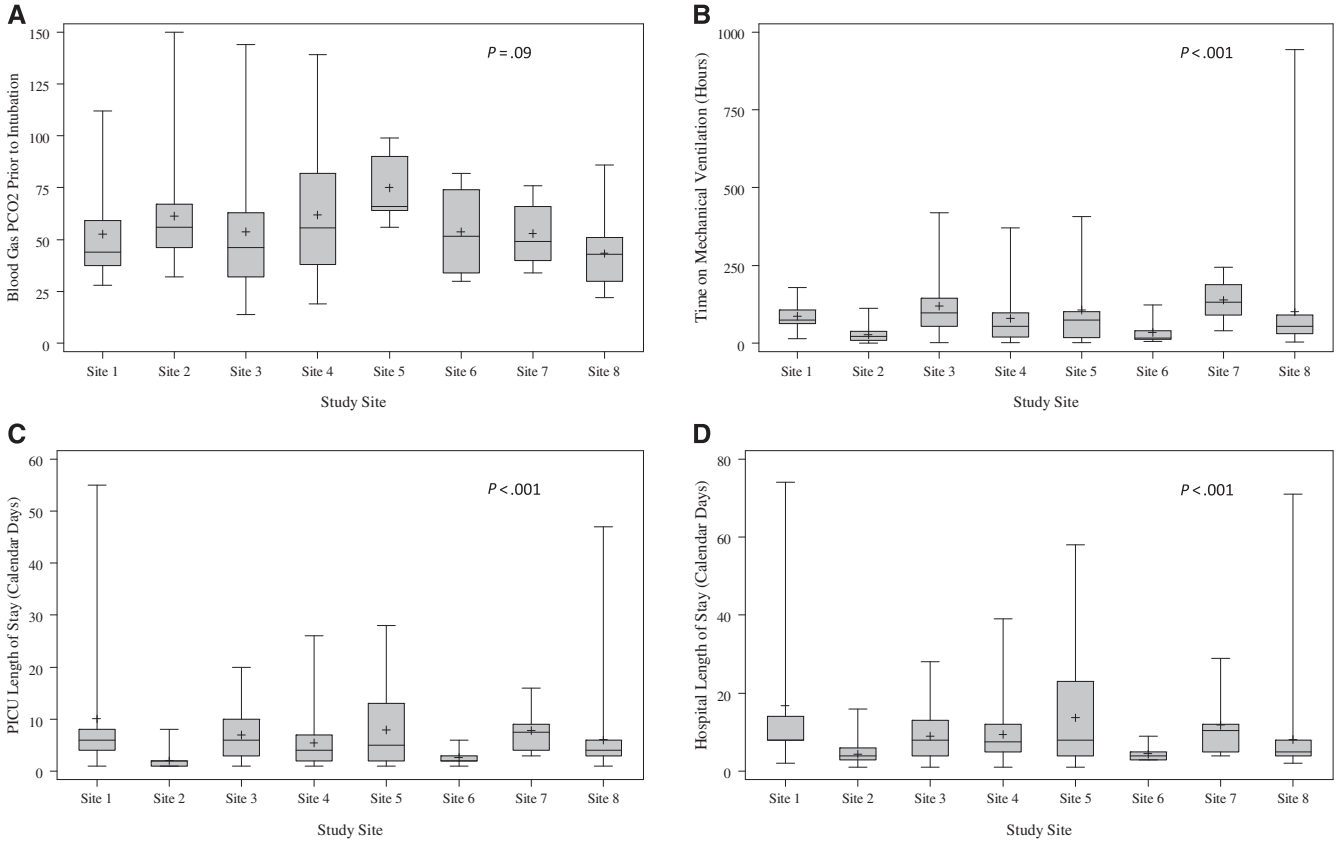

Figure 1. **A,** PCO_2 (arterial, capillary, or corrected venous [−6 torr]) before intubation, showing no differences among sites. Note that only 48% of patients had blood gas analyses obtained before intubation. **B,** LMV, showing significant differences among sites. **C,** PICU length of stay, showing significant differences among sites. **D,** Hospital length of stay, showing significant differences among sites. The mean (+), median (–), IQR (*box*), and range (*whiskers*) are plotted in each panel for each site. *P* values were obtained using the Wilcoxon rank-sum test and demonstrate overall differences among the CPCCRN PICUs for duration of PICU and hospital stays and LMV. No multiple-comparison tests were done to identify differences among PICUs.