Critical care for pediatric asthma: Wide care variability and challenges for study

Susan L. Bratton, MD, MPH; Christopher J. L. Newth, MD, FRCPC; Athena F. Zuppa, MD, MSCE; Frank W. Moler, MD, MS; Kathleen L. Meert, MD; Robert A. Berg, MD; John Berger, MD; David Wessel, MD; Murray Pollack, MD; Rick Harrison, MD; Joseph A. Carcillo, MD; Thomas P. Shanley, MD; Teresa Liu, MPH; Richard Holubkov, PhD; J. Michael Dean, MD; Carol E. Nicholson, MD, MS; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network

Objectives: **To describe pediatric severe asthma care, complications, and outcomes to plan for future prospective studies by the Collaborative Pediatric Critical Care Research Network.**

Design: **Retrospective cohort study.**

Setting: **Pediatric intensive care units in the United States that submit administrative data to the Pediatric Health Information System.**

Patients: **Children 1–18 yrs old treated in a Pediatric Health Information System pediatric intensive care unit for asthma during 2004–2008.**

Interventions: **None.**

Measurements and Main Results: **Thirteen-thousand five-hundred fifty-two children were studied; 2,812 (21%) were treated in a Collaborative Pediatric Critical Care Research Network and 10,740 (79%) were treated in a non-Collaborative Pediatric Critical Care Research Network pediatric intensive care unit. Medication use in individual Collaborative Pediatric Critical Care Research Network centers differed widely: ipratropium bromide (41%–84%), terbutaline (11%–74%), magnesium sulfate (23%–64%), and methylxanthines (0%–46%). Complications including pneumothorax (0%–0.6%), cardiac arrest (0.2%–2%), and aspiration (0.2%–2%) were rare. Overall use of medical therapies and complications at Collaborative Pediatric Critical Care Research Network centers were representative of pediatric asthma care at non-Collaborative Pediatric Critical Care Research Network pediatric intensive care units. Median length of pediatric intensive care unit stay at Collaborative Pediatric Critical Care Research Network centers was 1 to 2 days and death was rare (0.1%–3%). Ten percent of children treated at Collaborative Pediatric Critical Care Research Network centers received invasive mechanical ventilation compared to12% at non-Collaborative Pediatric Critical Care Research Network centers. Overall 44% of patients who received invasive mechanical ventilation were intubated in the pediatric intensive care unit. Children intubated outside the pediatric intensive care unit had significantly shorter median ventilation days (1 vs. 3), pediatric intensive care unit days (2 vs. 4), and hospital days (4 vs. 7) compared to those intubated in the pediatric intensive care unit. Among children who received mechanical respiratory support, significantly more (41% vs. 25%) were treated with noninvasive ventilation and significantly fewer (41% vs. 58%) were intubated before pediatric intensive care unit care when treated in a Pediatric Health Information System hospital emergency department.**

Conclusions: **Marked variations in medication therapies and mechanical support exist. Death and other complications were rare. More than half of patients treated with mechanical ventilation were intubated before pediatric intensive care unit care. Site of respiratory mechanical support initiation is associated with length of stay. (Pediatr Crit Care Med 2012; 13:000–000)**

KEY WORDS: asthma; heliox; magnesium sulfate; mechanical ventilation; methylxanthines; noninvasive ventilation; pediatric; terbutaline; variation

Asthma is the most common chronic disease of childhood, and although population-based rates of asthma-related hospital admission are decreasing (1), receipt of intensive care is increasing (2). National and international expert panels (3, 4) have enumerated stepwise care for chronic asthma with an emphasis on controller medication use and symptom based care plans (5, 6), but guidelines for critical childhood asthma care, defined as requiring admission to a pediatric intensive care unit (PICU), are not formally established.

Several factors limit advances to refine PICU asthma care. Currently, there is wide practice variation for care of the severely ill child with asthma (7–8). Furthermore,

From the University of Utah (SLB, RH, JMD, TL); Children's Hospital Los Angeles (CJN), Los Angeles, CA; Children's Hospital of Philadelphia (AFZ, RAB), Philadelphia, PA; University of Michigan (FWM, TPS); Children's Hospital of Michigan (KLM); Children's National Medical Center (JB, DW); Phoenix Children's Hospital (MP), Phoenix, AZ; University of California at Los Angeles (RH), Los Angeles, CA; Eunice Kennedy Shriver National Institute of Child Health and Human Development (CEN).

Supported, in part, by cooperative agreements (U10HD500009, U10HD050096, U10HD049981, U10HD049945, U10HD049983, U10HD050012, and U01HD049934) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Department of Health and Human Services.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: Susan.Bratton@hsc.utah.edu

DOI: 10.1097/PCC.0b013e318238b428

studies of pediatric critical asthma care are hampered by lack of a consistent and reproducible outcome measure. Most children cannot reliably perform pulmonary function testing during an exacerbation and mortality from severe asthma is rare. Reported outcomes include length of PICU stay, need for mechanical respiratory support (7, 9, 10), or toxicity from therapy (11–13). However, length of stay (LOS) is often affected by factors extraneous to the patient such as census, nurse staffing, and time of day, whereas need for intubation may be subjective.

Wide variation in care presents opportunities for improvement and research equipoise for future studies (14). The objective of this study was to describe current pediatric severe asthma care, complications, and outcomes to inform plans for future studies by the Collaborative Pediatric Critical Care Research Network (CPCCRN) (15). We evaluated PICU medical therapies and mechanical support for asthma care at the CPCCRN centers that submit data to the Pediatric Health Information System (PHIS) to determine whether therapies differed among CPCCRN centers. We also compared care between CPCCRN and non-CPCCRN centers to assess if the CPCCRN centers are representative of pediatric asthma care in U.S. free-standing children's hospitals that contribute to PHIS. Receipt of mechanical respiratory support, LOS, complications, and readmission were evaluated as potential outcomes for future severe asthma studies.

MATERIALS AND METHODS

Data Source. The CPCCRN (15) is a multicentered research network. We developed a critical asthma research design and development project to evaluate current practices and variability in asthma care through examination of PHIS, collected by Children's Health Corporation of America (CHCA) (16). CHCA is a collaboration of >40 children's hospitals, and PHIS contains administrative data including demographics, diagnoses, procedures, and charges. Six of eight CPCCRN sites contribute to PHIS (16). All PHIS data are de-identified and checked for reliability and validity before release. Clinical Transaction Classification is a proprietary system used by PHIS to categorize hospital billing for clinical, imaging, laboratory, pharmacy, supply, and other services. The centers for Medicare and Medicaid are adopting Clinical Transaction Classification for medication billing (17). However, the actual provision of a medication or service to a patient cannot be verified.

The University of Utah Institutional Review Board approved the study and granted waiver of informed consent. After approval, data for all children aged 1–18 yrs treated in a PHIS PICU from 2004 through 2008 with a primary diagnosis of asthma (International Classification Diseases version 9 codes 493.0, 493.1, 493.8, 493.81, 493.82, 493.9) were requested (18), and those with a diagnosis code for cystic fibrosis (codes 277.0, 277.00, or 277.02) or bronchiolitis (codes 466.1–466.19 or 487.1 or 491.8) were excluded.

Variables. Demographic information, admission source, daily asthma therapies, and laboratory/radiographic testing based on hospital charges while in the PICU were evaluated. Procedure codes for support therapies such as noninvasive positive airway pressure (93.90–93.99), tracheal intubation (96.04), mechanical ventilation (96.70–96.71), and complications such as air leak (512.1, 512, 770.2), aspiration (779.16), and cardiac arrest (427.5) were ascertained by International Classification Diseases version 9 codes (18) Readmission (emergency department, hospital ward, and PICU) for asthma after the initial PICU admission was tracked during the study period.

Outcomes. Receipt and duration of noninvasive and invasive ventilation, LOS in the PICU and hospital, duration of ventilation, complications, and mortality were evaluated. Tracheal intubation in the PICU was defined as either a procedure code for intubation or a procedure code for both noninvasive ventilation and invasive ventilation during the first PICU day. The PHIS database tracks procedures and charges by calendar day, and the assumption was made that noninvasive ventilation typically preceded invasive ventilation.

Analysis. Hospitals were designated as either CPCCRN or non-CPCCRN centers. Variation in asthma therapies between CPCCRN and non-CPCCRN centers was evaluated to determine whether the CPCCRN sites are representative of severe PICU asthma care in U.S. children's hospitals. Therapies, monitoring, and outcomes among CPCCRN centers were compared to evaluate patterns of care and to evaluate potential outcomes for clinical trials. Receipt of asthma therapies based on charges for medications and mechanical support were evaluated for all cases and the subset treated with either noninvasive or invasive ventilation. Data were described using median values with 25^{th} and 75^{th} quartiles or as percentages and were compared using the Kruskal-Wallis H test or the chi-square test. A Bonferroni adjustment for statistical significance was used when making multiple pair-wise comparisons of continuous data with the analysis regarding site of intubation; however, variation within CPCCRN centers was not tested for multiple comparisons, because variation across centers was the question of interest, not whether specific centers differed significantly from each other. Statistical significance was defined as $p < .05$ and all analyses were conducted using SPSS 14.0 for Windows (SPSS, Chicago, IL).

RESULTS

Thirteen-thousand five-hundred fifty-two children met study criteria in the PHIS dataset; of these, 2812 (21%) received care in a CPCCRN site. Select demographic and clinical features are compared within CPCCRN centers and between CPCCRN and non-CPCCRN centers in Table 1. Patients treated at most centers had a median age of 6 yrs and were predominantly male. Although race and ethnicity varied across centers, blacks and Hispanics were overrepresented compared to the American population census information (19). CPCCRN centers had fewer white (16% vs. 29%), more black (61% vs. 42%), and fewer Hispanic children (11% vs. 13%) than the non-CPCCRN centers. Government-sponsored insurance was the most common payer.

Although the majority of children were first treated in the PHIS hospital pediatric emergency department, this varied significantly among CPCCRN (33%–89%), and between CPCCRN and non-CPCCRN centers (75% vs. 66%). Median PICU stays were statistically different across CPCCRN centers but appeared clinically similar (median 1 or 2 days at each center). Complications in CPCCRN centers, including pneumothorax (0%–0.6%), cardiac arrest (0.2%–2%), aspiration (0.2%–2%), and death (0.2%–2%) were rare and similar overall to those of non-CPCCRN centers.

Table 2 compares asthma treatments across CPCCRN centers and between CPCCRN and non-CPCCRN centers. Because the study size is large, many therapies differed significantly between CPCCRN and non-CPCCRN centers but were clinically similar (e.g., intravenous terbutaline 24% vs. 21%, $p = .002$). However, administration of intravenous terbutaline varied substantially across CPCCRN centers (11%–74%). The database does not have information on dose; thus, escalation of inhaled or intravenous β2 agonists could not be evaluated. Use of inhaled anticholinergics (41%–84%), intravenous magnesium (23%–64%), and methylxanthines (0%–46%) all varied across CPCCRN centers, whereas between CPCCRN and non-CPCCRN centers only the use of inhaled anticholinergics (59% vs. 71%) and intravenous

Table 1. Select demographic and clinical features of children treated for acute asthma within Collaborative Pediatric Critical Care Research Network sites and comparing Collaborative Pediatric Critical Care Research Network to non-Collaborative Pediatric Critical Care Research Network

Feature	Collaborative Pediatric Critical Care Research Network Sites						Collaborative Pediatric Critical Care Research Network All N = 2812 n (%)	Non-Collaborative Pediatric Critical Care Research Network N = 10,740 n (%)
	A N = 341 n (%)	B N = 1402 n (%)	C N = 156 n (%)	D N = 471 n (%)	E N = 54 n (%)	F N = 388 n (%)		
Age, median yrs (interquartile range)	6 (3–10)	6 (3–10)	9 (4–144)	6 (3–12)	6 (3–10)	6 (3–9)	6 (3–11)[a]	6 (3–10)[b]
Male	190 (56)	886 (63)	103 (65)	306 (65)	240 (62)	35 (65)	1760 (63)[a]	6483 (60)[b]
Race								
White	155 (51)	98 (7)	7 (5)	61 (14)	128 (34)	2 (4)	451 (16)	3073 (29)
Black	117 (34)	1061 (78)	125 (80)	332 (77)	55 (15)	16 (30)	1706 (61)	4512 (42)
Hispanic	1 (0.3)	116 (9)	2 (1)	17 (4)	157 (42)	29 (54)	322 (11)	1395 (13)
Asian	1 (0.3)	15 (1)	0	4 (1)	2 (1)	4 (7)	26 (1)	150 (1)
Other	30 (10)	76 (6)	7 (5)	19 (4)	33 (9)	3 (6)	168 (6)	634 (6)
Unknown	37 (11)	36 (3)	15 (10)	38 (8)	13 (3)	0	139 (5)[a]	976 (9)[b]
Payer								
z	172 (50)	812 (58)	65 (42)	109 (23)	210 (54)	44 (82)	1412 (50)	5730 (53)
Private	132 (39)	587 (42)	24 (15)	90 (19)	153 (39)	0	986 (35)	2372 (22)
Other	0	2 (0.1)	54 (35)	232 (50)	1 (0.3)	10 (19)	299 (11)	1734 (16)
Unknown	37 (11)	1 (0.1)	13 (8)	40 (8)	24 (6)	0	155 (4)	904 (8)
Emergency department admission source	254 (75)	1247 (89)	102 (65)	357 (76)	129 (33)	31 (57)	2170 (75)[a]	7105 (66)[a]
Length of stay, median days (interquartile range)								
Length of stay	3 (2–4)	2 (1–3)	3 (2–4)	3 (2, 5)	3 (2–4)	4 (2–5)	2 (2–4)[a]	3 (2–4)[b]
Pediatric intensive care unit length of stay	1 (1–2)	2 (1–3)	1 (1–2)	2 (1–3)	1 (1–2)	2 (1–3)	1 (1–2)[a]	1 (1–2)[b]
Complications								
Pneumothorax	1 (0.3)	2 (0.1)	1 (0.6)	0	1 (0.3)	0	5 (0.4)	46 (0.2)
Pneumomediastinum	2 (1)	6 (0.4)	6 (4)	7 (2)	2 (1)	0	23 (0.9)[a]	110 (1)
Aspiration	3 (1)	3 (0.2)	2 (1)	4 (1)	2 (1)	1 (2)	15 (0.5)	36 (0.3)
Cardiac arrest	3 (1)	3 (0.2)	1 (1)	3 (1)	4 (1)	1 (2)	15 (0.5)	50 (0.5)
Death	1 (0.3)	1 (0.1)	1 (0.6)	1 (0.2)	4 (1)	1 (2)	9 (0.3)[a]	27 (0.3)

[a]$p < .05$ differs within Collaborative Pediatric Critical Care Research Network Centers; [b]$p < .05$ between Collaborative Pediatric Critical Care Research Network and non-Collaborative Pediatric Critical Care Research Network Centers.

magnesium (37% vs. 43%) differed by clinically important magnitudes.

Use of advanced respiratory support differed significantly across CPCCRN centers: heliox (0%–28%), noninvasive ventilation (0.3%–6%), and invasive ventilation (6%–26%). Comparison of CPCCRN and non-CPCCRN centers use of mechanical respiratory support was: heliox (15% vs. 8%), noninvasive ventilation (3% vs. 5%), and invasive ventilation (10% vs.12%). With the exception of heliox administration, use of mechanical support appeared to be clinically similar between CPCCRN and non-CPCCRN centers. Use of blood gas testing, chest radiography, and magnesium measurements varied significantly across CPCCRN centers, but overall use did not differ between CPCCRN and non-CPCCRN centers.

Readmission after the index admission was tracked for CPCCRN center patients and 12% were admitted to the pediatric hospital emergency department a median of 5 months later. Readmission to the hospital was even more common (17%) a median of 4 months later. Additionally, 6% were readmitted to the PICU a median of 4 months after the initial asthma PICU admission.

To evaluate children treated for the most severe asthma, a subgroup (n = 303) that received either noninvasive mechanical ventilation and/or invasive mechanical ventilation at a CPCCRN site are presented in Table 3 and Table 4. The median length of PICU stay varied significantly by site with a median range of 2 to 4 days; however, duration of invasive ventilation did not significantly differ across CPCCRN sites. Complications were relatively low: pneumothorax (0%–4%), aspiration (2%–11%), and cardiorespiratory arrest (2%–15%) did not differ significantly across CPCCRN sites. The mean mortality rate was 2%.

Therapies and monitoring in this subgroup are reported in Table 4. There was significant variation for treatment use across CPCCRN centers, including intravenous terbutaline (20%–85%), ipratropium bromide (22%–89%), intravenous magnesium sulfate (27%–62%), and methylxanthines (0%–56%). The proportion of children intubated before PICU care ranged from 43% to 87% across CPCCRN centers. Comparing CPCCRN to non-CPCCRN centers, significantly more were intubated before PICU care in CPCCRN centers (62% vs. 47%). Whereas similar proportions were intubated in a PICU (30% vs. 28%), use of noninvasive ventilation without invasive ventilation was more common at non-CPCCRN centers (8% vs. 25%). Testing blood gases and magnesium levels as well as radiographic imaging varied significantly across CPCCRN centers. Readmission after the initial PICU asthma admission in this subgroup was 9% to the emergency department, 16% to the hospital, and 6% to the PICU.

To more fully evaluate ventilatory support in PICU asthma care, all children (CPCCRN and non-CPCCRN centers) treated with noninvasive or invasive mechanical ventilation were stratified by site of endotracheal intubation and type of

Table 2. Therapies used to treat pediatric asthma within Collaborative Pediatric Critical Care Research Network sites and comparing Collaborative Pediatric Critical Care Research Network to non-Collaborative Pediatric Critical Care Research Network

Feature	Collaborative Pediatric Critical Care Research Network Sites						Collaborative Pediatric Critical Care Research Network All N = 2812 n (%)	Non-Collaborative Pediatric Critical Care Research Network N = 10,740 n (%)
	A N = 341 n (%)	B N = 1402 n (%)	C N = 156 n (%)	D N = 471 n (%)	E N = 388 n (%)	F N = 54 n (%)		
Medications in pediatric intensive care unit								
Steroids	307 (90)	1211 (86)	132 (85)	427 (91)	332 (86)	48 (89)	2475 (87)	9233 (86)
β-agonists								
Inhaled albuterol	312 (92)	1354 (97)	149 (96)	347 (74)	367 (95)	50 (93)	2579 (92)	9222 (86)
Inhaled lev-albuterol[a,b]	13 (4)	89 (6)	0	0	32 (8)	3 (6)	137 (5)	846 (8)
Inhaled albuterol and lev-albuterol[a,b]	9 (3)	62 (8)	0	0	23 (6)	3 (6)	97 (3)	647 (6)
Intravenous terbutaline[a,b]	69 (20)	150 (11)	26 (17)	347 (74)	46 (12)	29 (54)	667 (24)	2253 (21)
Inhaled albuterol and intravenous terbutaline[a]	64 (19)	150 (11)	26 (17)	262 (56)	44 (11)	29 (54)	575 (20)	2125 (20)
Inhaled ipratropium[a,b]	244 (72)	580 (41)	105 (67)	376 (80)	327 (84)	28 (52)	1660 (59)	7663 (71)
Magnesium[a,b]	129 (38)	316 (23)	100 (64)	247 (52)	230 (59)	25 (46)	1047 (37)	4620 (43)
Methylxanthines[a,b]	75 (22)	1 (0.1)	32 (21)	7 (2)	0	25 (46)	140 (5)	683 (6)
Antibiotics[a,b]	192 (56)	482 (34)	60 (39)	191 (41)	120 (31)	18 (33)	1063 (38)	4186 (39)
Neuromuscular blocking agent[a]	32 (9)	36 (3)	33 (21)	63 (13)	28 (7)	10 (19)	202 (7)	712 (7)
Mechanical support used in pediatric intensive care unit								
Heliox[a,b]	282 (23)	78 (6)	43 (28)	6 (1)	18 (5)	0	427 (15)	813 (8)
Noninvasive ventilation[a,b]	20 (6)	17 (3)	2 (1)	30 (6)	1 (0.3)	2 (4)	72 (3)	570 (5)
Invasive ventilation[a,b]	49 (14)	112 (8)	40 (26)	48 (10)	23 (6)	9 (17)	281 (10)	1258 (12)
Tests in pediatric intensive care unit, median (interquartile range)[c]								
N, blood gas[a]	1 (1–4)	2 (1–5)	1 (1–4)	2 (1–5)	2 (1–6)	4 (2–10)	2 (1–4)	2 (1–4)
N, x-rays[a]	1 (1–2)	2 (1–3)	1 (1–4)	2 (1–6)	1 (1–2)	4 (2–10)	2 (1–4)	2 (1–4)
N, magnesium[a,b]	1 (1–4)	3 (1–3)	1 (1–4)	2 (1–6)	2 (1–3)	5 (3–14)	2 (1–4)	2 (1–4)

[a] $p < .05$ differs within Collaborative Pediatric Critical Care Research Network centers; [b] $p < .05$ between Collaborative Pediatric Critical Care Research Network and non-Collaborative Pediatric Critical Care Research Network centers; [c] total tests during intensive care stay.

support (Table 5). Significantly more children (41% vs. 25%) were treated with noninvasive ventilation and significantly fewer (41% vs. 58%) were intubated before PICU care when treated in a PHIS hospital emergency department compared to other sites of pre-PICU care. Children treated with noninvasive ventilation were significantly older (median age, 8 yrs) than those intubated in the PICU without a trial of noninvasive ventilation (median age, 6 yrs).

Children intubated outside the PICU had significantly shorter PICU and hospital LOS compared to those treated solely with noninvasive ventilation. Forty percent of children (259/642) initially treated with noninvasive ventilator support progressed to invasive ventilation. The median duration of invasive ventilation was 3 days for children intubated in the PICU without a trial of noninvasive ventilation compared to 2 days for those intubated after noninvasive ventilation (not significantly different); however, LOS in the PICU was significantly less for those treated with a trial of noninvasive ventilation before intubation.

DISCUSSION

In this large cohort of children treated for asthma in a PICU, both medication use and mechanical support varied widely within the CPCCRN centers but, on average, the CPCCRN centers were representative of a large group of children's hospitals in the United States that contribute data to PHIS. There was large variation in care for children who responded to initial medication therapy as well as children who were nonresponders treated with mechanical ventilator support. Complications such as air leak syndrome, aspiration, and death were uncommon in both groups. PICU LOS differed by 1–2 days, but duration of ventilation did not differ across CPCCRN sites among patients treated with mechanical respiratory support. Intubation for mechanical ventilator support most commonly occurred outside the PICU, but those intubated in the PICU appeared to have more severe disease with longer PICU LOS and duration of mechanical support.

The current variation in critical asthma care reflects the lack of high-quality research for "best practice." The World Health Organization and the National Heart, Lung, and Blood Institute recommendations do not address critical care for asthma in detail and differ slightly in recommended "second tier" therapies (3, 4). After "recommended" therapies including supplemental oxygen, systemic corticosteroids, inhaled β2 agonists, and ipratropium, the panels recommend "consideration" of other therapies (3, 4), which are not prioritized and lack a pathway for stepwise escalation. Wide variation in severe asthma care previously has been reported (7, 8, 20, 21) and the CPCCRN centers on average appear to utilize asthma therapies in a manner representative of current national practice. The most prominent recent change in medication treatment for asthma is increased use of intravenous magnesium sulfate (8).

The overall use of intravenous β-agonists (terbutaline) in PHIS PICUs was 22% and varied widely. However, the National Heart, Lung, and Blood Institute expert asthma guidelines specifically categorize intravenous β2 agonist as a ther-

Table 3. Select demographic and clinical features of children treated with mechanical ventilatory support at a Collaborative Pediatric Critical Care Research Center

	Collaborative Pediatric Critical Care Research Network Sites						
Feature	A N = 50 n (%)	B N = 112 n (%)	C N = 41 n (%)	D N = 65 n (%)	E N = 26 n (%)	F N = 9 n (%)	All Collaborative Pediatric Critical Care Research Network N = 303 n (%)
Age,[a] median yrs (interquartile range)	7 (2–11)	5 (2–11)	12 (4–15)	9 (3–14)	7 (1–12)	9 (3–13)	7 (3–12)
Male	31 (62)	76 (68)	27 (66)	45 (69)	17 (65)	5 (57)	201 (66)
Payer[a]							
Government	26 (52)	65 (58)	19 (46)	15 (23)	11 (42)	6 (66)	142 (47)
Private	18 (36)	47 (42)	7 (17)	19 (29)	14 (54)	0	105 (35)
Other	0	0	14 (34)	27 (42)	0	3 (33)	44 (15)
Unknown	6 (12)	0	1 (2)	5 (8)	1 (4)	0	12 (4)
Ethnicity[a]							
White	17 (34)	9 (8)	3 (7)	11 (17)	8 (31)	1 (11)	49 (16)
Black	18 (36)	78 (70)	34 (83)	42 (65)	5 (19)	5 (55)	182 (60)
Hispanic	0	4 (4)	0	4 (6)	7 (27)	2 (22)	17 (6)
Asian	0	1 (1)	0	0	2 (8)	1 (11)	4 (1)
Other	9 (18)	10 (9)	3 (7)	4 (6)	3 (12)	0	29 (10)
Unknown	6 (12)	10 (9)	1 (2)	4 (6)	1 (4)	0	22 (7)
Length of stay, median days (interquartile range)							
Length of stay[a]	4 (3–7)	3 (2–6)	4 (3–6)	6 (4–9)	5 (3–7)	7 (2–10)	4 (3–7)
Pediatric intensive care unit length of stay[a]	3 (2–4)	3 (1–5)	2 (1–2)	4 (2–6)	3 (2–4)	3 (2–7)	3 (2–5)
Invasive ventilation[b]	3 (2–4)	2 (1–3)	2 (1–2)	4 (1–5)	2 (1–3)	2 (1–6)	2 (1–3)
Complications							
Pneumothorax	1 (2)	1 (1)	1 (2)	0	1 (4)	0	4 (1)
Pneumomediastinum	1 (2)	1 (1)	2 (5)	1 (2)	0	0	9 (3)
Aspiration	1 (2)	3 (3)	2 (5)	4 (6)	2 (8)	1 (11)	13 (4)
Cardiac arrest	3 (6)	3 (3)	1 (2)	2 (3)	4 (15)	1 (11)	14 (5)
Death[a]	1 (2)	1 (1)	1 (2)	1 (2)	3 (12)	0	7 (2)

[a]$p < .05$ varies within groups; [b]among intubated patients.

apy with no proven benefit above aerosolized administration and greater risk of toxicity (3). Isoproterenol is specifically identified as "not recommended" because of potential myocardial toxicity (22). A Cochrane review of 15 studies reported no evidence to support use of intravenous β2 agonists in emergency department patients, including adults and children, to prevent hospital admission (23). Of note, intravenous β2 agonists are commonly used outside the United States for severe asthma for PICU care (24) and systemic delivery of β2 agonists are believed to result in more consistent drug delivery than aerosolized medication through a ventilator to a patient with severely obstructed airways. The persistent marked variability provides clinical data supporting equipoise for future studies regarding optimal medications for severe asthma.

Noninvasive ventilation is a potential asthma care study intervention. A greater proportion of children treated in the PHIS hospital emergency department was started on noninvasive ventilation compared to children triaged outside the PHIS emergency department, which likely reflects respiratory therapy expertise as well as physician comfort with noninvasive ventilation in children. Forty percent of children started on noninvasive ventilation "failed" and were subsequently treated with invasive ventilation. Small studies report the feasibility of noninvasive ventilation for pediatric asthma (10, 25) and adults have rapid improvement in pulmonary function tests after institution of noninvasive ventilation (26). An initial trial of noninvasive ventilation did not increase PICU stay compared to children directly intubated in the PICU and was associated with decreased length of mechanical ventilator support. However, the lack of illness severity measurements limits conclusions regarding the efficacy of noninvasive ventilation to decrease the need for invasive ventilation.

Appropriate outcome measures for severe asthma studies require consideration. PICU LOS, mechanical ventilation, and complications are potential candidates but have limitations. Among our entire study group, the PICU LOS was a median of 1 day (interquartile range, 1–3). A child may be medically appropriate to transfer out of a PICU, but actual transfer depends on nonmedical factors such as nurse staffing and bed availability. PICU LOS differed more for the subset of children who received mechanical ventilator support, but duration of ventilation was significantly shorter for those intubated before admission to the PICU. Simple receipt of intubation therefore would be a poor outcome measure for studies of asthma therapy in the PICU. Complications such as air leak, aspiration, cardiac arrest, and death are uncommon outcomes even among the subset of children treated with mechanical respiratory support and would require a large study to have sufficient power to determine study intervention efficacy.

Although care variation can be ascribed in part to differences in illness severity, some of it is likely attributable to local practice patterns. Roberts et al (9) evaluated a multicentered retrospective cohort of children treated in intensive care units for asthma and reported that patient care differed between hospitals with physicians at some institutions more likely to intubate and mechanically ventilate children with similar $Paco_2$ and PRISM III scores. Our present data also document wide variability in blood sample testing, imaging studies, and administration of antibiotics (particularly

Table 4. Therapies used to treat children receiving mechanical ventilatory support in a Collaborative Pediatric Critical Care Research Center

Feature	Collaborative Pediatric Critical Care Research Network Sites						All Collaborative Pediatric Critical Care Research Network N = 303 n (%)
	A N = 50 n (%)	B N = 112 n (%)	C N = 41 n (%)	D N = 65 n (%)	E N = 26 n (%)	F N = 9 n (%)	
Medications							
Steroids	44 (88)	99 (88)	36 (88)	59 (91)	25 (96)	9 (100)	272 (90)
β-agonists							
Inhaled albuterol	48 (96)	106 (95)	38 (93)	54 (83)	24 (92)	9 (100)	279 (90)
Inhaled lev-albuterol[a]	1 (2)	14 (13)	0	0	6 (23)	0	21 (7)
intravenous terbutaline[a]	21 (42)	28 (25)	8 (20)	55 (85)	16 (62)	5 (56)	133 (44)
Inhaled albuterol and intravenous terbutaline[a]	21 (42)	28 (25)	8 (20)	45 (69)	14 (54)	5 (56)	121 (40)
Inhaled ipratropium[a]	35 (70)	45 (40)	27 (66)	57 (88)	23 (89)	2 (22)	189 (62)
Magnesium[a]	24 (48)	30 (27)	26 (63)	40 (62)	13 (50)	3 (33)	136 (45)
Methylxanthines[a]	18 (36)	1 (1)	13 (32)	5 (8)	0	5 (56)	42 (14)
Antibiotics[a]	40 (80)	59 (53)	18 (44)	46 (71)	21 (81)	5 (56)	189 (62)
Neuromuscular blocking agent[a]	30 (60)	32 (27)	32 (78)	38 (59)	20 (77)	9 (88)	160 (53)
Mechanical support							
Heliox[a]	41 (82)	23 (21)	14 (34)	2 (3)	1 (4)	0	81 (27)
Noninvasive only	3 (6)	0	1 (2)	17 (26)	3 (12)	0	24 (8)
Intubated in emergency department[a]	26 (52)	97 (87)	19 (46)	28 (43)	12 (46)	5 (56)	187 (62)
Intubated in pediatric intensive care unit[a,b]	21 (42)	15 (13)	20 (49)	20 (31)	11 (42)	4 (44)	92 (30)
Laboratory testing, median (interquartile range)[c]							
N, blood gases[a]	6 (3–12)	6 (2–20)	4 (1–7)	6 (3–25)	11 (5–19)	16 (5–48)	6 (2–16)
N, x-rays[a]	9 (2–16)	4 (2–17)	4 (1–6)	12 (4–31)	9 (4–17)	12 (5–45)	6 (2–16)
N, magnesium[a]	6 (3–16)	6 (2–12)	4 (1–5)	12 (2–24)	3 (2–6)		

[a]$p < .05$ within groups; [b]includes those with a trial of noninvasive and then intubated in the pediatric intensive care unit; [c]total tests during intensive care stay.

among patients who received mechanical support), but with similar clinical outcomes across centers.

Perhaps the most fundamental tool needed for development of meaningful severe asthma management research is a validated scoring system to aid assessment of disease severity and the need for increased therapy, and to improve consistency during care escalation and de-escalation. Although the National Institutes of Health Expert Panel for the "Guidelines for the Diagnosis and Management of Asthma" recommends use of peak flow meters to monitor response to therapy (3), many young or severely dyspneic children cannot perform such maneuvers. The Global Initiative for Asthma has a chart that includes physical findings, blood gas values, and peak expiratory flow rates to aid clinicians in asthma severity assessment but does not include a scoring system or recommendations for escalating care for increasing disease severity (4). Studies have not validated clinical asthma scoring systems to predict end points relevant for critical asthma such as response to therapy, mechanical support, or retention of carbon dioxide (22).

Although this study has the advantage of a very large sample of children treated in PICUs for a primary diagnosis of asthma, it has some limitations. Many physicians would expect 100% of children to receive corticosteroids and inhaled β2 agonists, which was not the case in our population. It is possible that some received corticosteroids and/or inhaled β-agonists but were not billed for those treatments, or the PICU stay was sufficiently short that doses administered in the emergency department were sufficient. Because exposure to various asthma treatments was based on billing, we also cannot be sure if the individual patient actually received the therapy. For example, the number of patients billed for NMBA was higher than the number billed for mechanical ventilation at several of the CPCCRN hospitals. Perhaps NMBAs were ordered to the bedside but were not administered to the patients because of clinical improvement. The Clinical Transaction Classification codes and billing data did not perfectly correspond with the International Classification Diseases version 9 procedure codes. A major limitation is that the pharmacy and procedure data are recorded daily rather than hourly, which prevents assessment of care escalation. Furthermore, the pharmacy data do not include dose or interval of administration. This precludes assessment of dose variation and escalation that can be large for inhaled β-agonists and intravenous terbutaline (14). Finally, lack of severity of illness measures limit conclusions regarding efficacy of therapy and differences in LOS by site of intubation.

This study supports previous observations that PICU asthma care varies widely between centers with marked variation in medication and mechanical support as well as testing. Mortality and complications such as air leak syndrome are uncommon and use of "rescue" therapies (e.g., inhaled anesthetic agents, extracorporeal membrane oxygenation) is rare. New information reported included data regarding duration of ventilation and LOS by site of intubation. Some variation in care may be partly attributable to disease severity, but it is also likely that some is attributable to local and physician practice patterns. A validated severity of asthma scoring system is important to document disease severity to develop and rigorously follow-up clinical management pathways to decrease care variation and hopefully improve outcomes. Timing of intubation, either before or during PICU admission, is associated with LOS and duration of ventilation and therefore should be considered as a potential confounding factor in future interventional trials. The current large variation in care for severe pediatric asthma provides equipoise to further study the impact of spe-

Table 5. Place of intubation and clinical features among mechanical support: All Pediatric Health Information System Centers

Feature	Noninvasive only N = 383 n (%)	Invasive Only Outside PICU Intubation N = 860 n (%)	Invasive Only Intubated in PICU N = 420 n (%)	Noninvasive Intubated in PICU N = 259 n (%)
Age,[a,b] median yrs (interquartile range)	8 (4–11)	7 (3–11)	6 (2–11)	8 (4–12)
Male[a]	213 (55)	534 (62)	269 (64)	152 (58)
Pediatric Health Information system emergency department source[a]	248 (64)	355 (41)	244 (58)	167 (65)
Complications				
Aspiration[a]	4 (1)	8 (1)	12 (3)	13 (5)
Pneumothorax[a]	0	17 (2)	16 (4)	4 (2)
Cardiac arrest[a]	0	33 (4)	20 (5)	2 (1)
Death[a]	1 (0.3)	19 (2)	13 (3)	0
Length of stay, median days (interquartile range)				
Pediatric intensive care unit length of stay[a,c]	2 (1–4)	2 (1–3)	4 (2–7)	3 (2–6)
Hospital length of stay[a,c]	4 (3–6)	4 (2–6)	7 (5–11)	5 (3–8)
Days noninvasive[a,e]	2 (1–3)	-	-	1 (1–2)
Days ventilation[a,d]	0	1 (1–2)	3 (2–6)	2 (1–4)
Therapies				
Steroids[a]	359 (94)	764 (89)	409 (97)	233 (90)
Inhaled albuterol[a]	353 (92)	762 (89)	369 (88)	221 (85)
Inhaled ipratropium[a]	305 (80)	579 (67)	281 (67)	207 (80)
Intravenous terbutaline[a]	167 (44)	249 (29)	229 (54)	84 (32)
Magnesium[a]	199 (52)	344 (40)	240 (57)	154 (60)
Methylxanthines[a]	57 (15)	94 (11)	85 (20)	28 (11)
Neuromuscular blocking agents[a]	28 (7)	265 (31)	367 (87)	74 (29)
Antibiotics[a]	192 (50)	269 (55)	344 (82)	183 (71)
Tests, median (interquartile range)				
N, blood gases[a,f]	4 (2–8)	4 (2–12)	20 (6–60)	6 (3–24)
N, x-rays[a,f]	4 (2–9)	4 (1–9)	16 (6–49)	6 (2–20)
N, electrolytes[a,g]	4 (2–9)	4 (1–9)	9 (4–23)	9 (7–36)
N, magnesium concentrations[a,g]	6 (2–12)	4 (2–12)	12 (4–32)	10 (4–36)
N, aminophylline concentrations[a,b]	2 (2–8)	6 (2–12)	11 (6–35)	8 (4–27)

[a]$p < .05$ across groups; [b]pair-wise comparison for noninvasive only vs. intubated and invasive ventilation in pediatric intensive care unit ($p < .008$); [c]all pair-wise comparisons differ significantly ($p < .008$) except noninvasive only vs. invasive only intubated outside pediatric intensive care unit; [d]pair-wise comparisons for invasive only intubated outside pediatric intensive care unit significantly different than for both groups intubated in pediatric intensive care unit ($p < .008$); [e]Pair-wise comparison for noninvasive significantly different than noninvasive and intubated in pediatric intensive care unit ($p < .008$); [f]all pair-wise comparisons significantly different ($p < .008$) except for noninvasive only and invasive only intubated outside the pediatric intensive care unit; [g]both groups intubated in pediatric intensive care unit significantly different than for noninvasive and invasive ventilation intubated outside the pediatric intensive care unit ($p < .008$).

cific treatment strategies on asthma outcomes and optimize care for this critically ill group of children.

ACKNOWLEDGMENTS

CPCCRN members participating in this study included: University of Utah (Data Coordinating Center), Salt Lake City, UT: J. Michael Dean, MD, MBA, Jeri Burr, MS, RN-BC, CCRC, Amy Clark, MS, Richard Holubkov, PhD, Stephanie Bisping, BSN, RN, CCRP, Teresa Liu, MPH, Rene Enriquez, BS; Children's National Medical Center, Washington, DC: John Berger, MD, David Wessel, MD, Jean Reardon, MA, BSN, RN; Children's Hospital of Pittsburgh, Pittsburgh, PA: Joseph Carcillo, MD, Michael Bell, MD, Alan Abraham, BA, CCRC; Children's Hospital of Michigan, Detroit, MI: Kathleen L. Meert, MD, Sabrina Heidemann, MD, Ann Pawluszka, BSN, RN; Children's Hospital Los Angeles, Los Angeles, CA: Christopher J. L. Newth, MD, FRCPC, J. Francisco Fajardo, CLS (ASCP), RN, MD; Mattel Children's Hospital at University of California Los Angeles, Los Angeles, CA: Rick Harrison, MD; The Children's Hospital of Philadelphia, Philadelphia, PA: Robert A. Berg, MD, Athena F. Zuppa, MD, MSCE, Mary Ann DiLiberto, BS, RN, CCRC; Phoenix Children's Hospital, Phoenix, AZ: Murray Pollack, MD, Heidi Dalton, MD, Christian Lawson, MS, RN, CPON; University of Michigan: CCRP, Thomas P. Shanley, MD. Frank W. Moler, MD, MS, Monica S. Weber, BSN, RN; Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD: Carol Nicholson, MD, MS, FAAP, Tammara Jenkins, MSN, RN.

REFERENCES

1. Moorman JE, Rudd RA, Johnson CA, et al: National Surveillance for Asthma—United States, 1980–2004. *MMWR Morb Mortal Wkly Rep* 2007; 56;1–14, 18–54
2. Hartman ME, Linde-Zwirble WT, Angus DC, et al: Trends in admissions for pediatric status asthmaticus in New Jersey over a 15-year period. *Pediatrics* 2010; 126:e904–e911
3. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Managing exacerbations of asthma. Available at:http://www.nhlbi.nih.gov/guidelines/asthma/11_sec5_exacerb.pdf. Accessed October 2, 2010
4. Management of asthma exacerbation in acute care settings. GINA at a glance management reference. Available at: http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=1920. Accessed October 2, 2010
5. Ducharme FM, Zemek RL, Chalut D, et al: Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med* 2011; 183:195–203
6. Zemek RL, Bhogal SK, Ducharme FM: Systematic review of randomized controlled trials examining written action plans in chil-

dren: What is the plan? *Arch Pediatr Adolesc Med* 2008; 162:157–163
7. Bratton SL, Odetola FO, McCollegan J, et al: Regional variation in ICU care for pediatric patients with asthma. *J Pediatr* 2005; 147: 355–361
8. Babl FE, Sheriff N, Borland M, et al: Paediatric acute asthma management in Australia and New Zealand: Practice patterns in the context of clinical practice guidelines. *Arch Dis Child* 2008; 93:307–312
9. Roberts JS, Bratton SL, Brogan TV, et al: Acute severe asthma: Differences in therapies and outcomes among pediatric intensive care units. *Crit Care Med* 2002; 30:581–585
10. Carroll CL, Smith SR, Collins MS, et al: Endotracheal intubation and pediatric status asthmaticus: Site of original care affects treatment. *Pediatr Crit Care Med* 2007; 8:91–95
11. Mitra A, Bassler D, Goodman K, et al: Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. *Cochrane Database Syst Rev*. 2005; 18:CD001276
12. Chiang VW, Burns JP, Rifai N, et al: Cardiac toxicity of intravenous terbutaline for the treatment of severe asthma in children: A prospective assessment. *J Pediatr* 2000; 137: 73–77
13. Bogie AL, Towne D, Luckett PM, et al: Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. *Pediatr Emerg Care* 2007; 23:355–361
14. Carroll CL, Schramm CM: Protocol-based titration of intravenous terbutaline decreases length of stay in pediatric status asthmaticus. *Pediatr Pulmonol* 2006; 41:350–356
15. Collaborative Pediatric Critical Care Research Network (CPCCRN) Eunice Kennedy Shriver National Institute of Child Health and Human Development. Available at: http://www.nichd.nih.gov/research/supported/CPCCRN.cfm. Accessed October 2, 2010
16. Children's Health Corporation of America: A business alliance of children's hospitals. Available at: http://chca.com/index_no_flash.html. Accessed October 2, 2010
17. Centers for Medicare and Medicaid Services: Transactions and Code Sets Regulations. Available at: http://www.cms.gov/TransactionCodeSetsStands/02_TransactionsandCodeSetsRegulations.asp. Accessed October 2, 2010
18. Online ICD9 codes. Available at: http://icd9cm.chrisendres.com. Accessed October 2, 2010
19. Population Information: Centers for Disease Control. Available at: http://wonder.cdc.gov/population.html. Accessed October 2, 2010
20. Bratton SL, Roberts JS, Watson RS, et al: Acute severe asthma: Outcome and Medicaid insurance. *Pediatr Crit Care Med* 2002; 3:234–238
21. Bratton SL, Roberts JS: Variation in the use of mechanical ventilation for asthma: How big a gap? *Pediatr Crit Care Med* 2007; 8:186–187
22. Maguire JF, O'Rourke PP, Colan SD, et al: Cardiotoxicity during treatment of severe childhood asthma. *Pediatrics* 1991; 88: 1180–1186
23. Travers A, Jones AP, Kelly K, et al: Intravenous 2-agonists for acute asthma in the emergency department. *Cochrane Database Syst Rev* 2001; (2):CD002988
24. Habashy D, Lam LT, Browne GJ: The administration of beta2-agonists for paediatric asthma and its adverse reaction in Australian and New Zealand emergency departments: A cross-sectional survey. *Eur J Emerg Med* 2003; 10:219–224
25. Mayordomo-Colunga J, Medina A, Rey C, et al: Predictive factors of non invasive ventilation failure in critically ill children: A prospective epidemiological study. *Intensive Care Med* 2009; 35:527–536
26. Soma T, Hino M, Kida K, et al: A prospective and randomized study for improvement of acute asthma by non-invasive positive pressure ventilation (NPPV). *Inter Med* 2008; 47: 493–501
27. Boluyt N, van der Lee JH, Moyer VA, et al: State of the evidence on acute asthma management in children: A critical appraisal of systematic reviews. *Pediatrics* 2007; 120: 1334–1343