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Critical Care for Pediatric Asthma: Wide Care Variability and Challenges for Study

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Abstract

Objective—To describe pediatric severe asthma care, complications and outcomes to plan for future prospective studies by the Collaborative Pediatric Critical Care Research Network (CPCCRN).

Design—Retrospective cohort study.

Setting—Pediatric intensive care units (PICU)s in the United States that submit administrative data to the Pediatric Health Information System (PHIS).

Patients—Children 1-18 years treated in a PHIS PICU for asthma during 2004 to 2008.

Interventions—None

Measurement and Main Results—13,552 children were studied; 2,812 (21%) treated in a CPCCRN and 10,740 (79%) in a non-CPCCRN PICU. Medication use in individual CPCCRN 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 CPCCRN centers were representative of pediatric asthma care at non-CPCCRN PICUs.

Median length of PICU stay at CPCCRN centers was 1 to 2 days and death was rare (0.1-3%). Ten percent of children treated at CPCCRN centers received invasive mechanical ventilation compared to 12 percent at non-CPCCRN centers. Overall 44% of patients who received invasive mechanical ventilation were intubated in the PICU. Children intubated outside the PICU had significantly shorter median ventilation days (1 vs.3), PICU days (2 vs. 4) and hospital days (4 vs. 7) compared

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to those intubated in the PICU. Among children who received mechanical respiratory support significantly more (41 vs. 25%) were treated with non-invasive ventilation and significantly fewer (41 vs. 58%) were intubated prior to PICU care when treated in a PHIS hospital emergency department.

Conclusions—Marked variations in medication therapies and mechanical support exist. Death and other complications were rare. Over half of patients treated with mechanical ventilation were intubated prior to PICU care. Site of respiratory mechanical support initiation is associated with length of stay.

Keywords

Asthma; mechanical ventilation; non-invasive ventilation; variation; pediatric; terbutaline; heliox; magnesium sulfate; methylxanthines

Introduction

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 step-wise 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, 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 while 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 is 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 if 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 US 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.

METHODS

Data Source

The CPCCRN (15) is a multi-center research network. We developed a critical asthma research design and development project to evaluate current practices and variability in asthma care through examination of Pediatric Health Information System (PHIS), collected by Children's Health Corporation of America (CHCA) (16). CHCA is a collaboration of more than 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 prior to release. Clinical Transaction Classification™ (CTC) 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 CTC 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 years treated in a PHIS PICU from 2004 through 2008 with a primary diagnosis of asthma (International Classification Diseases version 9(ICD9)-493.0, 493.1, 493.8, 493.81, 493.82, 493.9) were requested (18) and those with a diagnosis code for cystic fibrosis (277.0, 277.00 or 277.02) or bronchiolitis (466.1-466.19 or 487.1 or 491.8) 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 non-invasive 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 ICD9 codes (18) Readmission (ED, hospital ward and PICU) for asthma after the initial PICU admission was tracked during the study period.

Outcomes

Receipt and duration of non-invasive 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 non-invasive 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 non-invasive 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 if the CPCCRN sites are representative of severe PICU asthma care in US 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: 1) all cases and 2) the subset treated with either non-invasive or invasive ventilation. Data were described using median values with 25th and 75th inter-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 $p < 0.05$ and all analyses were conducted using SPSS 14.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

13,552 children met study criteria in the PHIS dataset; of these 2,812 (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 years and were predominantly male. Although race and ethnicity varied across centers, African Americans and Hispanics were over-represented 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 ED, 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 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. IV terbutaline 24% vs. 21%, $p=0.002$). However, administration of IV terbutaline varied substantially across CPCCRN centers (11% -74%). The database does not have information on dose; thus escalation of inhaled or intravenous β 2 agonists could not be evaluated. Use of inhaled anti-cholinergics (41-84%), IV magnesium (23-64%), and methylxanthines (0-46%) all varied across CPCCRN centers, while between CPCCRN and non-CPCCRN centers only the use of inhaled anti-cholinergics (59 vs. 71%) and IV magnesium (37 vs. 43%) differed by clinically important magnitudes.

Use of advanced respiratory support differed significantly across CPCCRN centers: heliox (0-28%), non-invasive 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%), non-invasive 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 ED 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.

In order to evaluate children treated for the most severe asthma, a subgroup (N=303) that received either non-invasive mechanical ventilation and/or invasive mechanical ventilation at a CPCCRN site are presented in Tables 3-4. 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: IV terbutaline (20-85%), ipratropium bromide (22-89%), IV magnesium sulfate (27-62%), and methylxanthines (0-56%). The proportion of children intubated prior to PICU care ranged from (43 – 87%) across CPCCRN centers. Comparing CPCCRN to non-CPCCRN centers, significantly more were intubated prior to PICU care in CPCCRN centers (62. vs. 47%). While similar proportions were intubated in a PICU (30 vs. 28%). Use of non-invasive 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.

In order to more fully evaluate ventilatory support in PICU asthma care, all children (CPCCRN and non-CPCCRN centers) treated with non-invasive or invasive mechanical ventilation were stratified by site of endotracheal intubation and type of support (Table 5). Significantly more children (41 vs. 25%) were treated with non-invasive ventilation and significantly fewer (41 vs. 58%) were intubated prior to PICU care when treated in a PHIS hospital ED compared to other sites of pre-PICU care. Children treated with non-invasive ventilation were significantly older (median age 8 years) than those intubated in the PICU without a trial of non-invasive ventilation (median age 6 years).

Children intubated outside the PICU had significantly shorter PICU and hospital LOS compared to those treated solely with non-invasive ventilation. Forty percent of children (259/642) initially treated with non-invasive 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 non-invasive ventilation compared to 2 days for those intubated after non-invasive ventilation (not significantly different); however, LOS in the PICU was significantly less for those treated with a trial of non-invasive ventilation prior to 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 US that contribute data to PHIS. There was large variation in care for both children who responded to initial medication therapy as well as children who were non-responders 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 (NHLBI) 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 β_2 agonists and ipratropium, the panels recommend "consideration" of other therapies, (3-4) which are not prioritized and lack a pathway for step-wise escalation. Wide variation in severe asthma care has previously 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 IV magnesium sulfate (8).

The overall use of IV β agonists (terbutaline) in PHIS PICUs was 22% and varied widely. However, the NHLBI expert asthma guidelines specifically categorize IV β_2 agonist as a therapy 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 IV β 2 agonists in emergency department patients, including adults and children, to prevent hospital admission (23). Of note, IV β 2 agonists are commonly used outside the United States for severe asthma for PICU care (24) and systemic delivery of β 2 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.

Non-invasive ventilation is a potential asthma care study intervention. A greater proportion of children treated in the PHIS hospital ED were started on non-invasive ventilation compared to children triaged outside the PHIS ED which likely reflects respiratory therapy expertise as well as physician comfort with non-invasive ventilation in children. Forty percent of children started on non-invasive ventilation “failed” and were subsequently treated with invasive ventilation. Small studies report the feasibility of non-invasive ventilation for pediatric asthma (10, 25) and adults have rapid improvement in pulmonary function tests after institution of non-invasive ventilation (26). An initial trial of non-invasive 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 non-invasive 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 non-medical 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 prior to admission to the PICU. Simple receipt of intubation would therefore 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 very 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* evaluated a multi-center retrospective cohort of children treated in ICUs 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 PaCO₂ and PRISM III scores (9). Our present data also document wide variability in blood sample testing, imaging studies, and administration of antibiotics (particularly 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, need for increased therapy, and to improve consistency during care escalation and de-escalation. Although the NIH 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 endpoints

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 pediatric ICUs for a primary diagnosis of asthma, it has some limitations. Many physicians would expect 100% of children to receive corticosteroids and inhaled β 2 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 ED 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 NMBA's were ordered to the bedside, but not administered to the patients because of clinical improvement. The CTC codes and billing data did not perfectly correspond with the ICD-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 does 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 length of stay 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, ECMO) rare. New information reported included data regarding duration of ventilation and LOS by site of intubation. Some variation in care may be due in part to disease severity but it is also likely that some is due to local and physician practice patterns. A validated severity of asthma scoring system is important to document disease severity in order to develop and rigorously follow clinical management pathways to decrease care variation and hopefully improve outcomes. Timing of intubation, either prior to or during a 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 specific treatment strategies on asthma outcomes and optimize care for this critically ill group of children.

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Table 1

Select Demographic and Clinical Features of Children Treated for Acute Asthma Within CPCCRN Sites and Comparing CPCCRN to Non-CPCCRN

Feature	CPCCRN Sites			CPCCRN			Non-CPCCRN		
	A	B	C	D	E	F	ALL		
	N=341	N=1402	N=156	N=471	N=388	N=54	N=2812	N=10740	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age (median yrs, IQR)	6 (3, 10)	6 (3, 10)	9 (4, 14)	6 (3, 12)	6 (3, 10)	6 (3, 9)	6 (3, 11) [#]	6 (3, 10) [*]	
Male	190 (56)	886 (63)	103 (65)	306 (65)	240 (62)	35 (65)	1760 (63) [#]	6483 (60)	
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)	976 (9)	
Payer							[#]	[*]	
Government	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)	
ED admission source	254 (75)	1247 (89)	102 (65)	357 (76)	129 (33)	31 (57)	2170 (75) [#]	7105 (66) [*]	
Length of stay (median days, IQR)									
LOS	3 (2, 4)	2 (1, 3)	3 (2, 4)	3 (2, 5)	3 (2, 4)	4 (2, 5)	2 (2, 4) [#]	3 (2, 4) [*]	
PICU LOS	1 (1, 2)	2 (1, 3)	1 (1, 2)	2 (1, 3)	1 (1, 2)	2 (1, 3)	1 (1, 2) [#]	1 (1, 2) [*]	
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) [#]	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) [#]	27 (0.3)	

$p < 0.05$ differs within CPCCRN Centers

* $p < 0.05$ between CPCCRN and non-CPCCRN Centers

Emergency department (ED), length of stay (LOS), intensive care unit (PICU)

Table 2
Therapies Used to Treat Pediatric Asthma Within CPCCRN Sites and Comparing CPCCRN to Non-CPCCRN

Feature	CPCCRN Sites				CPCCRN		Non-CPCCRN	
	A	B	C	D	E	F	ALL	
	N=341	N=1402	N=156	N=471	N=388	N=54	N=2812	N=10740
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Medications in PICU								
Steroids	307(90)	1211(86)	132(85)	427(91)	332(86)	48 (89)	2475 (87)	9233 (86)
<i>β</i> agonists								
Inhaled albuterol	312(92)	1354(97)	149(96)	347(74)	367(95)	50 (93)	2579 (92)	9222 (86)
Inhaled lev-albuterol ^{##}	13 (4)	89 (6)	0	0	32 (8)	3 (6)	137 (5)	846 (8)
Inhaled alb & lev-albuterol	9 (3)	62 (8)	0	0	23 (6)	3 (6)	97 (3)	647 (6)
IV terbutaline ^{##}	69 (20)	150 (11)	26 (17)	347 (74)	46 (12)	29 (54)	667 (24)	2253 (21)
Inhaled albuterol & IV terbutaline [*]	64 (19)	150 (11)	26 (17)	262(56)	44 (11)	29 (54)	575 (20)	2125 (20)
Inhaled ipratropium ^{##}	244(72)	580 (41)	105(67)	376(80)	327(84)	28 (52)	1660 (59)	7663 (71)
Magnesium ^{##}	129(38)	316 (23)	100(64)	247(52)	230(59)	25 (46)	1047 (37)	4620 (43)
Methylxanthines ^{##}	75 (22)	1 (0.1)	32 (21)	7 (2)	0	25 (46)	140 (5)	683 (6)
Antibiotics ^{##}	192(56)	482 (34)	60 (39)	191(41)	120(31)	18 (33)	1063 (38)	4186 (39)
NMBA [*]	32 (9)	36 (3)	33 (21)	63 (13)	28 (7)	10 (19)	202 (7)	712 (7)
Mechanical Support used in PICU								
Heliox ^{##}	282(23)	78 (6)	43 (28)	6 (1)	18 (5)	0	427 (15)	813 (8)
Non-invasive ventilation ^{##}	20 (6)	17 (3)	2 (1)	30 (6)	1 (0.3)	2 (4)	72 (3)	570 (5)
Invasive ventilation ^{##}	49 (14)	112 (8)	40 (26)	48 (10)	23 (6)	9 (17)	281 (10)	1258 (12)
Tests in PICU (median,IQR) ^τ								
N, blood gas [*]	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 [*]	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 ^{##}	1 (1, 4)	3 (1, 3)	1 (1, 4)	2 (1, 6)	2 (1, 3)	5(3,14)	2 (1, 4)	2 (1, 4)

^{*} p < 0.05 differs within CPCCRN centers

^{##} p < 0.05 between CPCCRN and non-CPCCRN centers

τ total tests during intensive care stay

Lev albuterol (lev alb), terbutaline (IV terb), neuromuscular blocking agent (NMBA)

Select Demographic and Clinical Features of Children Treated with Mechanical Ventilatory Support at a Collaborative Pediatric Critical Care Research Center

Table 3

Feature	CPCCRN Sites					
	A	B	C	D	E	F
	N=50	N=112	N=41	N=65	N=26	N=9
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age* (median yrs, IQR)	7 (2, 11)	5 (2, 11)	12 (4, 15)	9 (3, 14)	7 (1, 12)	9 (3, 13)
Male	31 (62)	76 (68)	27 (66)	45 (69)	17 (65)	5 (57)
Payer*						
Gov	26 (52)	65 (58)	19 (46)	15 (23)	11 (42)	6 (66)
Private	18 (36)	47 (42)	7 (17)	19 (29)	14 (54)	0
Other	0	0	14 (34)	27 (42)	0	3 (33)
Unknown	6 (12)	0	1 (2)	5 (8)	1 (4)	0
Ethnicity*						
White	17 (34)	9 (8)	3 (7)	11 (17)	8 (31)	1 (11)
Black	18 (36)	78 (70)	34 (83)	42 (65)	5 (19)	5 (55)
Hispanic	0	4 (4)	0	4 (6)	7 (27)	2 (22)
Asian	0	1 (1)	0	0	2 (8)	1 (11)
Other	9 (18)	10 (9)	3 (7)	4 (6)	3 (12)	0
Unknown	6 (12)	10 (9)	1 (2)	4 (6)	1 (4)	0
Length of Stay (median days, IQR)						
LOS*	4 (3, 7)	3 (2, 6)	4 (3, 6)	6 (4, 9)	5 (3, 7)	7 (2, 10)
PICU LOS*	3 (2, 4)	3 (1, 5)	2 (1, 2)	4 (2, 6)	3 (2, 4)	3 (2, 7)
Invasive ventilation τ	3 (2, 4)	2 (1, 3)	2 (1, 2)	4 (1, 5)	2 (1, 3)	2 (1, 6)
Complications						
Pneumothorax	1 (2)	1 (1)	1 (2)	0	1 (4)	0
Pneumomediastinum	1 (2)	1 (1)	2 (5)	1 (2)	0	0
Aspiration	1 (2)	3 (3)	2 (5)	4 (6)	2 (8)	1 (11)
Cardiac arrest	3 (6)	3 (3)	1 (2)	2 (3)	4 (15)	1 (11)
Death*	1 (2)	1 (1)	1 (2)	1 (2)	3 (12)	0

*
 $p < 0.05$ varies within groups
 τ among intubated patients

Government (gov), length of stay (LOS), intensive care unit (PICU), conventional ventilator (ventilation)

Therapies Used to Treat Children Receiving Mechanical Ventilatory Support in a Collaborative Pediatric Critical Care Research Center

Table 4

Feature	CPCCRN Sites				All CPCCRN			
	A	B	C	D	E	F		
	N=50	N=112	N=41	N=65	N=26	N=9	N=303	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Medications								
Steroids	44 (88)	99 (88)	36 (88)	59 (91)	25 (96)	9 (100)	272 (90)	
<i>β</i> agonists								
Inhaled albuterol	48 (96)	106 (95)	38 (93)	54 (83)	24 (92)	9 (100)	279 (90)	
Inhaled lev-albuterol *	1 (2)	14 (13)	0	0	6 (23)	0	21 (7)	
IV terbutaline *	21 (42)	28 (25)	8 (20)	55 (85)	16 (62)	5 (56)	133 (44)	
Inhaled albuterol & IV terbutaline *	21 (42)	28 (25)	8 (20)	45 (69)	14 (54)	5 (56)	121 (40)	
Inhaled ipratropium *	35 (70)	45 (40)	27 (66)	57 (88)	23 (89)	2 (22)	189 (62)	
Magnesium *	24 (48)	30 (27)	26 (63)	40 (62)	13 (50)	3 (33)	136 (45)	
Methylxanthines *	18 (36)	1 (1)	13 (32)	5 (8)	0	5 (56)	42 (14)	
Antibiotics *	40 (80)	59 (53)	18 (44)	46 (71)	21 (81)	5 (56)	189 (62)	
NMBA *	30 (60)	32 (27)	32 (78)	38 (59)	20 (77)	9 (88)	160 (53)	
Mechanical Support								
Heliox *	41 (82)	23 (21)	14 (34)	2 (3)	1 (4)	0	81 (27)	
Non-invasive only	3 (6)	0	1 (2)	17 (26)	3 (12)	0	24 (8)	
Intubated in ED *	26 (52)	97 (87)	19 (46)	28 (43)	12 (46)	5 (56)	187 (62)	
Intubated in PICU * [‡]	21 (42)	15 (13)	20 (49)	20 (31)	11 (42)	4 (44)	92 (30)	
Laboratory Testing (median, IQR) [#]								
N, blood gases *	6 (3, 12)	6 (2, 20)	4 (1, 7)	6 (3, 25)	11 (5, 19)	16 (5, 48)	6 (2, 16)	
N, x-rays *	9 (2, 16)	4 (2, 17)	4 (1, 6)	12 (4, 31)	9 (4, 17)	12 (5, 45)	6 (2, 16)	
N, magnesium *	6 (3, 16)	6 (2, 12)	4 (1, 5)	12 (2, 24)	3 (2, 6)	15 (5, 85)	6 (2, 16)	

* p < 0.05 within groups

[‡] includes those with a trial of non-invasive and then intubated in the PICU

total tests during intensive care stay

Lev-albuterol (lev alb), terbutaline (IV terb), neuromuscular blocking agent (NMBA), emergency department (ED), pediatric intensive care unit (PICU)

Table 5

Place of Intubation and Clinical Features among Mechanical Support: All PHIS Centers

Feature	Non-invasive Only N=383 n (%)	Invasive Only Outside PICU Intubation N=860 n (%)	Invasive Only Intubated in PICU N=420 n (%)	Non-Invasive Intubated in PICU N=259 n (%)
Age ^{*§} (median yrs, IQR)	8 (4, 11)	7 (3, 11)	6 (2, 11)	8 (4, 12)
Male [*]	213 (55)	534 (62)	269 (64)	152 (58)
PHIS ED Source [*]	248 (64)	355 (41)	244 (58)	167 (65)
Complications				
Aspiration [*]	4 (1)	8 (1)	12 (3)	13 (5)
Pneumothorax [*]	0	17 (2)	16 (4)	4 (2)
Cardiac Arrest [*]	0	33 (4)	20 (5)	2 (1)
Death [*]	1 (0.3)	19 (2)	13 (3)	0
Length of Stay (median days, IQR)				
PICU LOS ^{*τ}	2 (1, 4)	2 (1, 3)	4 (2, 7)	3 (2, 6)
Hospital LOS ^{*τ}	4 (3, 6)	4 (2, 6)	7 (5, 11)	5 (3, 8)
Days non invasive ^{*α}	2 (1, 3)	-	-	1 (1, 2)
Days ventilation ^{*κ}	0	1 (1, 2)	3 (2, 6)	2 (1, 4)
Therapies				
Steroids [*]	359 (94)	764 (89)	409 (97)	233 (90)
Inhaled albuterol [*]	353 (92)	762 (89)	369 (88)	221 (85)
Inhaled ipratropium [*]	305 (80)	579 (67)	281 (67)	207 (80)
IV verbutaline [*]	167 (44)	249 (29)	229 (54)	84 (32)
Magnesium [*]	199 (52)	344 (40)	240 (57)	154 (60)
Methylxanthines [*]	57 (15)	94 (11)	85 (20)	28 (11)
Neuromuscular blocking agents [*]	28 (7)	265 (31)	367 (87)	74 (29)
Antibiotics [*]	192 (50)	269 (55)	344 (82)	183 (71)
Tests (median, IQR)				

Feature	Non-invasive Only N=383 n (%)	Invasive Only Outside PICU Intubation N=860 n (%)	Invasive Only Intubated in PICU N=420 n (%)	Non-Invasive Intubated in PICU N=259 n (%)
N, blood gases ^{*γ}	4 (2, 8)	4 (2, 12)	20 (6, 60)	6 (3, 24)
N, x-rays ^{*γ}	4 (2, 9)	4 (1, 9)	16 (6, 49)	6 (2, 20)
N, electrolytes ^{*β}	4 (2, 9)	4 (1, 9)	9 (4, 23)	9 (7, 36)
N, magnesium concentrations ^{*β}	6 (2, 12)	4 (2, 12)	12 (4, 32)	10 (4, 36)
N, aminophylline concentrations [*]	2 (2, 8)	6 (2, 12)	11 (6, 35)	8 (4, 27)

^{*} p < 0.05 across groups

^δ pair-wise comparison for non-invasive only vs. intubated & invasive ventilation in PICU, (p<0.008)

^τ all pair wise comparisons differ significantly (p<0.008) except non-invasive only versus invasive only intubated outside PICU.

^κ pair-wise comparisons for invasive only intubated outside PICU significantly different than both groups intubated in PICU, (p<0.008)

^α pair-wise comparison for non-invasive significantly different than non-invasive and intubated in PICU (p<0.008)

^γ all pair wise comparisons significantly different (p<0.008) except for non-invasive only and invasive only intubated outside the PICU

^β both groups intubated in PICU significantly different than non-invasive and invasive ventilation intubated outside the PICU, (p<0.008)

Pediatric Health Information System (PHIS), length of stay (LOS), intensive care unit (PICU), intravenous (IV), non-invasive ventilation (non-invasive)