Variability in Usual Care Mechanical Ventilation for Pediatric Acute Respiratory Distress Syndrome: Time for a Decision Support Protocol?*

Christopher J. L. Newth, MD, FRCPC[1,2]; Katherine A. Sward, PhD, RN[3,4]; Robinder G. Khemani, MD, MsCI[1,2]; Kent Page, MStat[5]; Kathleen L. Meert, MD[6]; Joseph A. Carcillo, MD[7]; Thomas P. Shanley, MD[8]; Frank W. Moler, MD[8]; Murray M. Pollack, MD[9]; Heidi J. Dalton, MD[9]; David L. Wessel, MD[10]; John T. Berger, MD[10]; Robert A. Berg, MD[11]; Rick E. Harrison, MD[12]; Richard Holubkov, PhD[5]; Allan Doctor, MD[13]; J. Michael Dean, MD[4,5]; Tammara L. Jenkins, MSN, RN[14]; Carol E. Nicholson, MD[15]; on behalf of the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN)

***See also p. 1075.**

[1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA.

[2]Department of Pediatrics, University of Southern California, Keck School of Medicine, Los Angeles, CA.

[3]University of Utah College of Nursing, Salt Lake City, UT.

[4]Department of Biomedical Informatics, University of Utah School of Medicine, Salt Lake City, UT.

[5]Department of Pediatrics, Division of Pediatric Critical Care, University of Utah School of Medicine, Salt Lake City, UT.

[6]Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI.

[7]Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA.

[8]Department of Pediatrics, University of Michigan, Ann Arbor, MI.

[9]Department of Child Health, Phoenix Children's Hospital, Phoenix, AZ.

[10]Department of Pediatrics, Children's National Medical Center, Washington, DC.

[11]Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA.

[12]Department of Pediatrics, Mattel Children's Hospital, UCLA, Los Angeles, CA.

[13]Departments of Pediatrics and Biochemistry, Washington University School of Medicine, St. Louis, MO.

[14] Pediatric Trauma and Critical Illness Branch, National Institutes of Child Health and Human Development (NICHD), Bethesda, MD.

[15] Formerly Pediatric Trauma and Critical Illness Branch, National Institutes of Child Health and Human Development (NICHD), Bethesda, MD.

Supported, in part, by the following cooperative agreements from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services: U10HD050096, U10HD049981, U10HD049983, U10HD050012, U10HD063108, U10HD063106, U10HD063114 and U01HD049934 and R21HD061870 awarded to Drs. Newth and Sward for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article; and decision to submit the article for publication.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

All authors have received support for article research from the National Institutes of Health (NIH). Dr. Sward's institution received funding from the National Institute of Child Health and Human Development (NICHD). Dr. Khemani received funding from Orange Medical (consultant). Dr. Page's institution received funding from the NICHD. Dr. Meert's institution received funding from the NIH. Dr. Carcillo's institution received funding from the NIH. Dr. Shanley's institution received funding from the NIH. Dr. Moler's institution received funding from the NIH/NICHD and from Health Resources and Services Administration. Dr. Pollack's institution received funding from the NIH. Dr. Dalton's institution received funding from the NIH and the NICHD Collaborative Pediatric Critical Care Research Network, and she received funding from Innovative ECMO Concepts Inc (consultant) and Maquet Inc (speaker). Dr. Wessel's institution received funding from the NIH. Dr. Berger's institution received funding from the NIH and the Association for Pediatric Pulmonary Hypertension. Dr. Harrison's institution received funding from the NIH. Dr. Holubkov's institution received funding from the NIH, and he received funding from St. Jude Medical (statistical consulting), Pfizer Inc (Data Safety Monitoring Board membership), and DURECT corporation (statistical consulting). Dr. Doctor's institution received funding from the NIH, the Department of Defense (U.S. Government), and the Children's Discovery Institute. Dr. Dean's institution received funding from the NICHD. Ms. Jenkins disclosed government work. Dr. Nicholson disclosed government work.

For information regarding this article, E-mail: cnewth@chla.usc.edu

DOI: 10.1097/PCC.0000000000001319

Objectives: Although pediatric intensivists philosophically embrace lung protective ventilation for acute lung injury and acute respiratory distress syndrome, we hypothesized that ventilator management varies. We assessed ventilator management by evaluating changes to ventilator settings in response to blood gases, pulse oximetry, or end-tidal Co_2. We also assessed the potential impact that a pediatric mechanical ventilation protocol adapted from

National Heart Lung and Blood Institute acute respiratory distress syndrome network protocols could have on reducing variability by comparing actual changes in ventilator settings to those recommended by the protocol.

Design: Prospective observational study.

Setting: Eight tertiary care U.S. PICUs, October 2011 to April 2012.

Patients: One hundred twenty patients (age range 17 d to 18 yr) with acute lung injury/acute respiratory distress syndrome.

Measurements and Main Results: Two thousand hundred arterial and capillary blood gases, 3,964 oxygen saturation by pulse oximetry, and 2,757 end-tidal Co_2 values were associated with 3,983 ventilator settings. Ventilation mode at study onset was pressure control 60%, volume control 19%, pressure-regulated volume control 18%, and high-frequency oscillatory ventilation 3%. Clinicians changed Fio_2 by ±5 or ±10% increments every 8 hours. Positive end-expiratory pressure was limited at ~10 cm H_2O as oxygenation worsened, lower than would have been recommended by the protocol. In the first 72 hours of mechanical ventilation, maximum tidal volume/kg using predicted versus actual body weight was 10.3 (8.5–12.9) (median [interquartile range]) versus 9.2 mL/kg (7.6–12.0) ($p < 0.001$). Intensivists made changes similar to protocol recommendations 29% of the time, opposite to the protocol's recommendation 12% of the time and no changes 56% of the time.

Conclusions: Ventilator management varies substantially in children with acute respiratory distress syndrome. Opportunities exist to minimize variability and potentially injurious ventilator settings by using a pediatric mechanical ventilation protocol offering adequately explicit instructions for given clinical situations. An accepted protocol could also reduce confounding by mechanical ventilation management in a clinical trial. (*Pediatr Crit Care Med* 2017; 18:e521–e529)

Key Words: acute lung injury; clinical protocols; conventional mechanical ventilation; decision support systems, high-frequency oscillatory ventilation

Ventilator management for children with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (now known collectively as pediatric ARDS or PARDS) is suspected to vary between institutions (1) and between pediatric intensivists (2). Clinicians treating adults generally accept National Institutes of Health/National Heart Lung and Blood Institute ARDS Network (ARDSNet) ventilator protocols (3) which have improved outcomes (3–5), but protocol implementation is not yet widespread (6, 7). Few ventilator protocols exist for pediatrics although studies of ALI in children (8–10) have used protocols described as similar to ARDSNet protocols (3).

Protocols developed in the adult ICU may need modification for the PICU (11). Pediatric intensivists commonly use different modes of mechanical ventilation (MV) than adult intensivists. There are unanswered questions including the magnitude of changes to Fio_2 and positive end-expiratory pressure (PEEP) and the acceptable range of permissive hypercapnia (11). Hence, we modified the ARDSNet protocol tables to develop a PARDS MV protocol (2, 12).

In the eight PICUs of the Collaborative Pediatric Critical Care Research Network (CPCCRN), we sought to determine "usual care" ventilator management practices in ALI/ARDS not guided by a protocol and to ascertain the potential applicability of our pediatric MV protocol. We hypothesized that there would be wide variability in usual care practice and inconsistency in MV decisions. We implemented a prospective, observational study to determine the frequency and scale at which intensivists changed ventilator settings. We compared these decisions against those recommended in our MV protocol to determine if use of the protocol could potentially decrease variability and increase more conservative decision-making for similar clinical situations.

METHODS

For detailed Methods, see **Supplemental Methods** (Supplemental Digital Content 1, http://links.lww.com/PCC/A518).

Institutional Review Board approval with waiver of consent was obtained for each site and the Data Coordinating Center (DCC). Eligibility criteria were MV via an endotracheal tube (ETT) or tracheotomy and three of the four diagnostic criteria for ALI/ARDS (acute onset of disease, at least two consecutive Pao_2/Fio_2 [P/F] ratios < 300 or two oxygen saturation by pulse oximetry (Spo_2)/Fio_2 [S/F] ratios < 260 within 12 hr of initiation of ventilation, and no left ventricular dysfunction). The fourth criterion is bilateral infiltrates on chest film, but this was not used for inclusion because of perceived subjectivity and interobserver variability (13). Exclusion criteria were heart failure; uncorrected cyanotic heart disease; an ETT leak greater than or equal to 20% (the difference between inspired and exhaled tidal volume (VT), measured at the ETT with a pneumotachometer); a lack of volume, pressure, and flow measurements at the ETT, or the patient was receiving extracorporeal membrane oxygenation therapy.

Data were collected from October 2011 to April 2012 from 15 patients at each site). During this time, there were no targeted MV strategies in place at any of the participating PICUs (14).

Data Extraction

The first P/F ratio less than 300 or S/F ratio less than 260 after MV through an ETT or tracheotomy defined the beginning of the study for each patient. We extracted from the medical record blood gas values at least four times daily along with ventilator changes. We collected data for 7 days or until extubation or death (whichever was first). S/F ratios were included only if the Spo_2 values were less than 98% (15). We associated ventilator settings with blood gas values based on time stamps. We analyzed patients supported by all conventional ventilation (CV) modalities (pressure control [PC], volume control [VC], pressure-regulated volume control [PRVC]) and high-frequency oscillatory ventilation (HFOV).

Pediatric ALI/ARDS MV Protocol

Our pediatric ALI/ARDS MV protocol for conventional modes was modified from ARDSNet protocol tables (3) using preliminary data and expert review by intensivists from CPCCRN and

the Pediatric Acute Lung Injury and Sepsis Investigators network. The HFOV protocol was based on a protocol developed in adults (16) where increasing amplitude rather than decreasing frequency is promoted as the lung protective strategy in situations of significant acidosis.

The protocol contains decision tables that implement ventilation strategies through discrete, explicit steps. Oxygenation tables evaluate combinations of PEEP (or mean airway pressure [MAP] in the case of HFOV) and F_{IO_2} stratified into high, mid, and low oxygenation (Pa_{O_2} and Sp_{O_2}) subsets. The adult protocol tables are based on F_{IO_2} increments of 0.1; this was reduced to 0.05 (for conventional modes, see **Supplemental Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/PCC/A519–**legend**, Supplemental Digital Content 8, http://links.lww.com/PCC/A525; and for HFOV mode, see **Supplemental Fig. 2**, Supplemental Digital Content 3, http://links.lww.com/PCC/A520–legend, Supplemental Digital Content 8, http://links.lww.com/PCC/A525).

Ventilation tables describe combinations of ventilatory support, stratified by pH, for the different modes of CV. When pH is less than 7.30, additional stratification is based on ventilatory rate (VR, breaths/min, BPM). Pediatric intensivists recommended 25 BPM as a stratification point (compared with 35 BPM in the ARDSNet protocol). The protocol for PC mode (the predominant one used in this study) is shown in **Supplemental Table 1** (Supplemental Digital Content 4, http://links.lww.com/PCC/A521).

Data Preparation and Comparison With the MV Protocol

We used the pediatric MV protocol to group data for analysis. Combinations of blood gas and ventilator data ranges define data bins with a treatment recommendation. Data were entered into a secure electronic data capture system (OpenClinica, Waltham, MA) maintained at the DCC (University of Utah, Salt Lake City, UT). We compared the protocol recommendations with the actual clinical care changes.

We used descriptive statistics to analyze initial blood gas and ventilator settings, times between PEEP and F_{IO_2} changes, transfers between CV and HFOV, and the variability of usual care regarding oxygenation and ventilation modes. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Gary, NC).

RESULTS

We analyzed 3,983 ventilator settings from 120 patients (age range 17 d to 18 yr with no preterm infants) and were able to associate ventilator settings with 1,943 arterial blood gas, 157 capillary blood gas, 3,964 SpO_2, and 2,757 end-tidal C_{O_2} ($PETC_{O_2}$) values (**Table 1**). All patients met three of the four criteria for ALI, and 62% of the patients had bilateral pulmonary infiltrates (meeting all four ALI criteria) reported at some stage of their illness. Only 38% had quadrants of infiltrates described in radiology reports. On study entry, the median P/F ratio was 128 and the S/F ratio was 162. The PALICC criteria for PARDS were devised after our study was performed. However, of the 120 patients enrolled, in the first 24 hours of MV, 87 had an oxygenation index greater than or equal to 4 or oxygenation saturation index greater than or equal to 5, thus meeting the new criteria. Ventilation mode at study onset was PC 60%, VC 19%, PRVC 18%, and HFOV 3%. Overall mortality was 13.3%; the median length of MV was 6.5 days; the median number of 28-day ventilator-free days was 19.4 days (Table 1).

Initial blood gas and ventilator settings are described in **Table 2**, and the extent of changes and times between peak inspiratory pressure (PIP), V_T, PEEP, and F_{IO_2} settings are shown in **Table 3**. The median time difference from blood gas to ventilator setting being recorded was 37 minutes. Descriptive statistics of the numbers of increases and decreases of F_{IO_2} and PEEP (all conventional modes) during selected study days is delineated (Supplemental Table 3, Supplemental Digital Content 6, http://links.lww.com/PCC/A523). On CV modes (PC, VC & PRVC), the median interval between ventilator changes was 4 hours.

The variability of usual care regarding oxygenation was examined with box plots of PEEP stratified by F_{IO_2} (**Fig. 1**). The PC mode was used for 51% of observations. In order to evaluate variability in ventilation, we calculated the direction of changes to either PIP or VR after a blood gas for each of the 18 data bins in the PC ventilation table (**Supplemental Table 2**, Supplemental Digital Content 5, http://links.lww.com/PCC/A522) as well as concordance of clinical care with what the protocol would have recommended (Supplemental Table 1, Supplemental Digital Content 4, http://links.lww.com/PCC/A521).

Changes in F_{IO_2} and PEEP on CV Modes

F_{IO_2} was changed a median of once per day on days 1, 2, 3, and 7 (**Supplemental Table 3**, Supplemental Digital Content 6, http://links.lww.com/PCC/A523) with the most common step size being ±0.05, followed closely by ±0.1 (Table 3). For patients in whom F_{IO_2} was changed more than once per day, the median time between F_{IO_2} changes was ~4 hours (Table 3). The mean highest PEEP was 9.2 cm H_2O. No change in PEEP was made for most patients on any given study day (Supplemental Table 3, Supplemental Digital Content 6, http://links.lww.com/PCC/A523). When changed, the most common alteration was ±1 cm H_2O followed by ±2 cm H_2O (47% and 41% of all PEEP changes, respectively).

Regardless of the Pa_{O_2} or Sp_{O_2} range (high, middle, low), clinicians were more likely to change F_{IO_2} than PEEP, resulting in considerable variability in the amount of F_{IO_2} used across different levels of PEEP (Fig. 1). Clinicians used higher F_{IO_2} and lower PEEP than the protocol would have recommended, particularly when F_{IO_2} exceeded 0.6. When F_{IO_2} was 0.6 or less, the PEEP level generally corresponded with the protocol (Fig. 1).

Changes in PIP and VR

For all modes of CV, PIP was less than or equal to 35 cm H_2O in 92% of observations and 99% were less than or equal to 40 cm H_2O. Median VR was 20 BPM, and 70% of values were less than 25 BPM with 4% greater than 35 BPM.

When comparing ventilator settings with the PC protocol, there was a median of 21 (interquartile range [IQR] 11–50)

TABLE 1. Demographics and Outcomes of Patients

Variables	Count	%	Median	IQR
Gender (male)	61	50.8		
Age (yr)	120	100.0	2.0	0.5–9.0
Weight (kg)	120	100.0	11.5	6.3–29.6
Height (cm)	82	68.3	80.5	59.0–112.0
Race				
White	64	53.3		
Black	29	24.2		
Other	27	22.5		
Ethnicity				
Hispanic or Latino	23	19.2		
Not Hispanic or Latino	53	44.2		
Unknown	44	36.7		
Chest films	618	100.0		
Patients with no report of bilateral infiltrates	46	38.3		
Patients with no report of quadrant infiltrates	74	61.7		
Number ventilator records	3,983			
Number ventilator changes	3,863			
ABG	1,943			
Patients with ABG	88	73.3		
CBG	157			
Patients with CBG	27	22.5		
Number oxygen saturation by pulse oximetry records	3,964			
Number end-tidal Co_2 records	2,757			
Mortality (died)	16	13.3		
Length mechanical ventilation (d)[c]	113[a]	94.2	6.5	3.5–11.5
28-d ventilator-free days	120[b]	100	19.4	8.6–23.4

ABG = arterial blood gases; CBG = capillary blood gases, IQR = interquartile range.
[a]Excludes seven patients discharged on mechanical ventilation.
[b]Includes data from the 16 dead patients (assumes ventilator-free days = 0).
[c]Noninvasive ventilation not included.

observations per cell (Supplemental Table 2, Supplemental Digital Content 5, http://links.lww.com/PCC/A522). Clinician response varied within each cell, with intensivists most commonly making no change (median, 56.2%; IQR, 46.2–58.5) (Supplemental Table 1, Supplemental Digital Content 4, http://links.lww.com/PCC/A521; and Supplemental Table 2, Supplemental Digital Content 5, http://links.lww.com/PCC/A522). This was true even when the PIP was greater than 35 cm H_2O, and the pH was greater than 7.45 (46%) or between 7.30–7.45 (62%). Forty-three per cent (466) of the 1,091 observations had a PIP greater than 28 cm H_2O (with 17% being above 35 cm H_2O). The ventilator protocol would have recommended reducing the PIP in 72% of these scenarios, but in practice, PIP (or VR) was decreased in only 25%. In most cases, no change was made, and in 14%, the PIP was actually increased.

Using a VR of greater than 25 BPM to assign cells, intensivists made changes similar to protocol recommendations 29% of the time, opposite to the protocol's recommendation 12% of the time and (in contrast to the program's recommendation) no changes 56% of the time.

Changes in Exhaled V_T

The mean exhaled VT at study entry was 7.4 mL/kg actual body weight (ABW) (Table 2). Over the course of ventilation, the VT averaged 7.1 (5.9–8.4) mL/kg ABW (median [IQR]). For PC mode, VT was 7.2 (5.7–9.0), and for VC and PRVC modes together, it was 7.1 (6.0–8.0) mL/kg.

TABLE 2. Descriptive Statistics of Initial Ventilator Settings and Blood Gases Obtained Within 6 Hr Following Study Entry

Variables	Count	%	Median	IQR
Pao_2/Fio_2 O_2 ratio	37		128.3	94.0–211.4
Spo_2/Fio_2 O_2 ratio	60		162.0	115.2–228.8
Oxygenation index	29		12.0	7.9–18.1
Oxygenation saturation index	36		7.9	4.8–12.5
Positive end-expiratory pressure (cm H_2O)	115		7.0	5.0–10.0
Peak inspiratory pressure (cm H_2O)	115		27.0	23.0–32.0
Mean airway pressure (cm H_2O)	82		13.0	11.0–16.0
Tidal volume exhaled (mL/kg)[a]	110		7.4	6.0–8.5
Ventilatory rate (breaths/min)	116		24.0	20.0–30.0
Fio_2	116		0.6	0.4–0.8
pH	45		7.31	7.21–7.36
Partial pressure of arterial Co_2 and partial pressure of capillary Co_2 (mm Hg)	45		43.3	38.4–48.0
End-tidal Co_2 (mm Hg)	70		38.0	31.0–48.0
Ventilator modes				
Pressure control	72	60.0		
Volume control	23	19.2		
Pressure-regulated volume control	21	17.5		
High-frequency oscillatoy ventilation	4	3.3		

IQR = interquartile range.

[a]Exhaled tidal volume measured at the endotracheal tube. This value was then divided by actual body weight to report tidal volume (mL/kg).

All ventilation modes excluding high-frequency oscillatoy ventilation–some missing values, particularly oxygen saturation by pulse oximetry (Spo_2)/Fio_2 O_2 ratios after study entry where $Spo_2 > 97\%$.

There were 80 patients (66.7% of total) where both height/length and weight were recorded and for whom a predicted body weight (PBW) could be calculated (Relcore, Los Angeles, CA). One PICU used ulna length (17, 18) for height prediction where the child had contractures or marked scoliosis. Using PBW resulted in higher V_T (V_T/kg) than ABW ($p < 0.001$), irrespective of whether the highest (9.2 [7.6–12.0] mL/kg ABW vs 10.3 [8.5–12.9] mL/kg PBW) or lowest (5.1 [4.0–6.5] mL/kg ABW vs 5.8 [4.2–7.1] mL/kg PBW) (median [IQR]), V_T was used.

Intersite Variability in Conventional Ventilator Management

To assess how sites embraced permissive hypercapnia, we examined the subset of patients managed with PC ventilation who had severe ARDS (P/F ratio < 100 or S/F ratio < 150). When plotting the pH, PIP, and V_T (**Fig. 2**) on days 1, 2, 3 and 7, there was a progressive decline in PIP, an increase in pH, and consistency of V_T at approximately 7.5 mL/kg over the first 3 days. By day 7, the V_T had risen to ~11 mL/kg. When stratifying by site (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/PCC/A519), there was wide variation in pH values with similar PIP values and vice versa. At least one site was significantly different from another in the application of PIP, pH, and V_T/kg (Kruskal-Wallis test $p < 0.001$ for each).

We examined the pattern of ventilation index (VI) with either VR or PIP change. There was a modest increase in VI when pH was below 7.40. VI did not change between pH 7.40 and 7.55 and then decreased again as the pH rose above 7.55. These differed from the CPCCRN protocol which recommends no change in VI for pH range 7.30–7.45 and a decrease in VI at pH greater than 7.45.

Changes on HFOV Mode

Four patients (3.3%) began the study on HFOV mode with a further 13 patients (10.8%) switching to it during the study. Ten of the 17 patients switched back to conventional modes. There were 444 recordings of HFOV ventilator settings with the most frequent decision being "No Change." The distribution of MAP with Fio_2 is shown in Supplemental Figure 2 (Supplemental Digital Content 3, http://links.lww.com/PCC/A520). The last settings before changing modes between CV and HFOV and back are shown in **Supplemental Tables 4, *A* and *B*** (Supplemental Table 2, Supplemental Digital Content 7, http://links.lww.com/PCC/A524).

TABLE 3. Magnitudes of Changes and Times Between Increases and Decreases of F_{IO_2} and Selected Ventilator Settings for Conventional Modes

Variables	Count	Median	IQR
Time between ventilator settings (hr)			
Time between F_{IO_2} increases (hr)	431	4.5	2.0–11.8
Extent of F_{IO_2} increases	431	0.10	0.05–0.2
Time between F_{IO_2} decreases (hr)	799	3.8	1.6–7.3
Extent of F_{IO_2} decreases	799	−0.10	−0.10 to −0.05
Time between PEEP increases (hr)	173	5.5	1.9–14.9
Extent of PEEP increases (cm H_2O)	173	2.0	1.0–2.0
Time between PEEP decreases (hr)	285	10.5	4.5–21.5
Extent of PEEP decreases (cm H_2O)	285	−1.0	−2.0 to −1.0
Time between PIP increases (hr)	685	4.2	2.3–7.0
Extent of PIP increases (cm H_2O)	685	2.0	1.0–5.0
Time between PIP decreases (hr)	906	4.1	2.2–7.4
Extent of PIP decreases (cm H_2O)	906	−2.0	−4.0 to −1.0
Time between tidal volume increases (hr)	898	4.1	2.5–6.6
Extent of tidal volume increases (mL/kg)	898	0.8	0.4–1.6
Time between tidal volume decreases (hr)	955	4.0	2.4–6.6
Extent of tidal volume decreases (mL/kg)	955	−0.8	−1.5 to −0.4
Time between ventilatory rate increases (hr)	222	5.3	2.4–12.0
Extent of ventilatory rate increases (BPM)	222	4.0	2.0–8.0
Time between ventilatory rate decreases (hr)	565	7.0	3.3–15.0
Extent of ventilatory rate decreases (BPM)	565	−4.0	−5.0 to −2.0

BPM = breaths/min, IQR = interquartile range, PEEP = positive end-expiratory pressure, PIP = peak inspiratory pressure.

DISCUSSION

This analysis demonstrated that intensivists, faced with children in similar states with ALI/ARDS, are inconsistent in their decisions about ventilatory support. Most notably, clinicians did not decrease F_{IO_2} when the Pa_{O_2} or Sp_{O_2} was in a high range. Intensivists used low levels of PEEP and high levels of F_{IO_2} when Pa_{O_2} and Sp_{O_2} were low. This appears consistent with earlier reports (2, 19). Furthermore, high peak pressures and VRs were frequently not decreased, even when the pH was greater than 7.45 (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/PCC/A519).

We used our pediatric MV protocol to examine variability in clinician decision-making. We evaluated the potential ability of the protocol to reduce any such variability by comparing actual changes with changes the protocol would have recommended given the same patient state. We evaluated the direction, but not size, of change. If the protocol is actually representative of best available evidence, then times when clinician responses differed from protocol recommendations might represent missed opportunities to improve lung protective ventilation practices. All protocols "must allow" for the fact that higher pressures and volumes do occur in clinical practice, and the protocols should suggest a pathway to wean a patient safely back to more protective settings. The protocol will recommend increasing PIP above 28 cm H_2O only if the pH is less than 7.15. The PIP is never escalated above 35 cm H_2O. Our data showed that PIP was escalated above 28 cm H_2O in 43% of the 1,091 observations. The ventilator protocol would have recommended reducing the PIP in 72% of these scenarios, but in practice, it was done in only 25%. Hence, the recommendations of the protocol appear to decrease pressures more consistently than observed practice.

This pediatric MV protocol has not yet been formally validated against clinically important outcomes such as ventilator-free days or mortality. Its actual benefits are unknown, and validation studies are needed (20).

Prior to prospective studies, the protocol must first be acceptable to intensivists (21). From our analysis, the behavior of intensivists was directly contradictory to the protocol's recommendations only 12% of the time. This relatively low rate of direct contradiction suggests that the protocol is, in general, consistent with current practice and likely acceptable to pediatric intensivists. Clinicians could have been responding

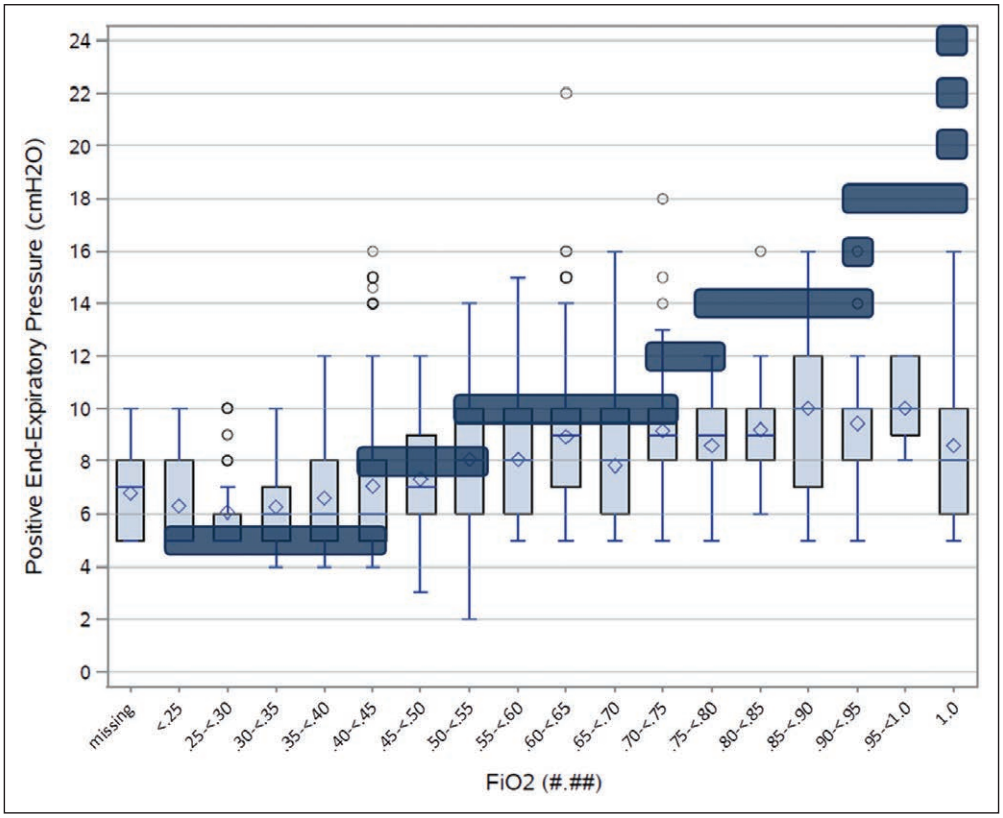

Figure 1. Box plot of positive end-expiratory pressure (PEEP)/F_{IO_2} combinations on all patients on conventional ventilation modes in the eight Collaborative Pediatric Critical Care Research Network (CPCCRN) PICUs. PEEP/F_{IO_2} titration tables from clinical care for all 120 patients on conventional modes of mechanical ventilation. The *y*-axis represents actual PEEP values as a function of actual F_{IO_2} used (*x*-axis). The superimposed dark blue boxes represent the pediatric mechanical ventilation protocol target combinations of PEEP/F_{IO_2}, derived from the Acute Respiratory Distress Syndrome Network protocols. For all patients, there is variability in PEEP/F_{IO_2} combinations intensivists choose. In general, clinicians use less PEEP (peaking at just under 10 cm H_2O) than the protocol would recommend, particularly when F_{IO_2} climbs above 0.6. 1) Actual CPCCRN data (*light blue boxes*), mean value (◇), median (*bar*), interquartile range (*box*), range (*whiskers*), outliers (○), protocol targets (*dark blue bars*). 2) Missing values are for 15 of the 3,504 PEEP/F_{IO_2} observations for which no F_{IO_2} was recorded. In addition, there were 26 observations excluded where no PEEP was recorded.

to changes in continuous Sp_{O_2} or PET_{CO_2} measurements rather than blood gases, as pulse oximetry and capnography were routinely used. Future studies should consider continuous ventilator, Sp_{O_2} and PET_{CO_2} data collection techniques, so that these apparent contradictions can be evaluated.

We identified a need to refine certain protocol recommendations such as the VR stratification at 25 BPM. In the adult protocol, this was intended to apply to a limited number of decisions where the patient was severely ill and aggressive change was needed. Pediatric intensivists escalated VR above 25 BPM in 28% of cases though only 4% of the time above 35 BPM. Perhaps, the original cut off of 35 BPM is appropriate for pediatrics as well. This may also be the case for our reduction of F_{IO_2} step changes to 0.05, as many pediatric physicians appeared comfortable with 0.1 changes.

Another potential contributing factor to variability in ventilator settings is determining which weight should be used to standardize measurements related to MV (e.g., functional residual capacity, compliance, and VT). In a recent study of 325,325 PICU, patients' height was recorded only 39% of the time (22). In our study, it appeared that ABW was used to calculate exhaled V_T and other variables, since height was recorded in only two thirds of cases. There was a wide variation of exhaled V_T and a median of 1.3 mL/kg above the low V_T target (6 mL/kg) in the ARDSNet study (3). Ward et al (23) undertook a retrospective data analysis from ARDS patients amalgamated from four studies and found underutilization of low V_T, particularly in overweight children, in the first 24 hours. Our prospective study confirms and expands the finding over 7 days. Additionally, V_T as measured in some ventilators is lower than the real volume (24). Investigation of measured lung volumes, compared with those calculated from ABW versus PBW in children, and whether the PBW use has an effect on PARDS outcomes, is a priority (25). Provocatively, a recent meta-analysis (26) suggested that unlike the ARDSNet trial in adults, V_T is not associated with mortality in pediatrics.

In this study, only 17 patients (14.2%) were placed on HFOV. This is consistent with earlier observations (1, 27–29) that HFOV is used only in about 10% of children with ARDS and reinforces the view that pediatric HFOV is reserved as a "rescue" modality for patients failing CV. In our study, it appeared that once a patient stabilized, little change was made to any HFOV variable save for inspired oxygen. Since variability seems less of an issue in HFOV mode, it may be that using decision support tools such as ours could decrease pressures more quickly and consistently with even less potential for lung injury.

The adult Berlin (30) and Pediatric Acute Lung Injury Consensus Conference (PALICC) (31) definitions of ARDS require the presence of bilateral or new pulmonary infiltrates, respectively, on chest radiograph and the Pediatric Lung Injury Score (32, 33) requires quadrants of disease. The low frequency of reporting of these abnormalities questions the relevance of this information in the scoring systems, although it is possible that intensivists read the films directly rather than relying on radiology reports.

Some may consider it a limitation that we analyzed PIP rather than plateau pressures. However, in the CPCCRN group, pressure-regulated modes (PC or PRVC) were most commonly used. Given the differing flow profile of delivered gas in these

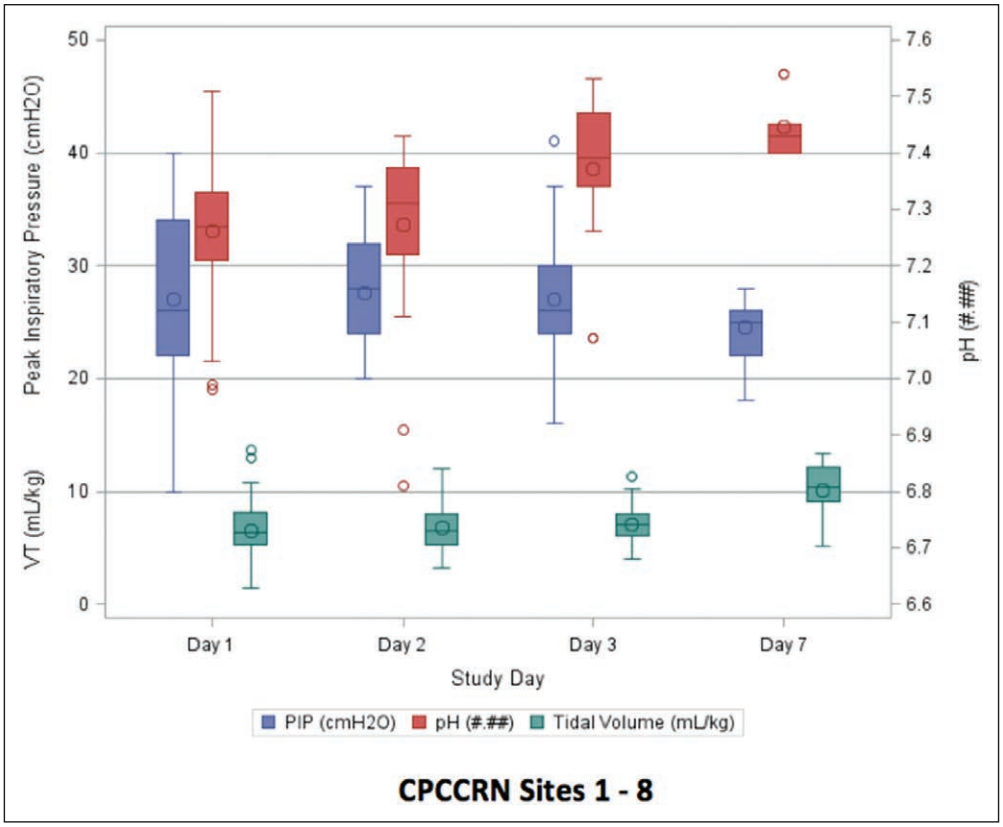

Figure 2. The distribution of peak inspiratory pressure (PIP), pH, and tidal volume (V_T)/kg actual body weight (ABW) averaged for all eight Collaborative Pediatric Critical Care Research Network (CPCCRN) sites over days 1, 2, 3, and 7 when treating patients with severe ARDS—Pao_2/Fio_2 ratio < 100 or oxygen saturation by pulse oximetry (Spo_2)/Fio_2 ratio < 150. The *y*-axis on the left shows the PIP (upper) and the V_T (mL/kg) (lower) values, and on the right, the pH values over the first 3 days of MV and day 7, for all CPCCRN sites and all patients with severe acute respiratory distress syndrome (ARDS). 1) V_T were maintained in the 7–8 mL/kg range for this group of patients with severe pediatric ARDS over the first 3 days. The resolution of disease over the week is implied by decreasing peak pressures and rising pHs with V_T having increased up to approximately 11 mL/kg ABW. 2) Mean value (◇), median (*bar*), interquartile range (*box*), range (*whiskers*), outliers (○).

modes from VC, plateau pressure and PIP are nearly always the same except in circumstances of significant elevations in airway resistance. Given these patients had PARDS, previous studies have shown that is not expected (34, 35).

Our analysis has limitations in that we could not elucidate the reasons for clinician decisions with respect to ventilator or oxygenation changes. It is possible that intensivists used data outside of the parameters in the ventilator protocol (i.e., such as hemodynamic variables or work of breathing) in their decisions to change or not change ventilator settings. It is also possible that the CPCCRN group of PICUs may not be representative of either American or international practice. However, the clear trends and consistent findings from a large number of observations from over 50 critical care physicians in eight PICUs give strength to our conclusions. In addition, the publication of the PALICC guidelines in June 2015 (31) subsequent to our study may also have begun to reduce variability even without the aid of a specific protocol.

CONCLUSIONS

Although pediatric intensivists have philosophically embraced lung protective ventilation for children with ARDS, ventilator management varies substantially with many apparent lost opportunities to minimize potentially injurious ventilator settings. An accepted ventilator management protocol (20) might encourage less variability and more systematic decisions about reductions in pressures and volumes. However, a randomized, controlled trial is needed to determine if adherence to such a protocol leads to a better outcome.

ACKNOWLEDGMENTS

We wish to acknowledge the contributions of the following individuals for their dedication and care in the documentation of the patients enrolled in this study: Julie Beckstrom, MPH, CCRP, University of Utah; Stephanie Bisping, BSN, RN, CCRP, University of Utah; Jean Reardon, MA, BSN, RN, Children's National Medical Center; Aimee Labell, MS, RN, Phoenix Children's Hospital; Jeffrey Terry, MBA, Children's Hospital Los Angeles; Margaret Villa, RN, Children's Hospital Los Angeles and Mattel Children's Hospital; Jeni Kwok, JD, Children's Hospital Los Angeles and Mattel Children's Hospital; Ann Pawluszka, BSN, RN, Children's Hospital of Michigan; Mary Ann DiLiberto, BS, RN, CCRC, Children's Hospital of Philadelphia; Monica S. Weber, RN, BSN, CCRP, University of Michigan; Alan C. Abraham, BA, CCRC, University of Pittsburgh Medical Center; and Jeri Burr, MS, RN-BC, CCRN, University of Utah. We also thank Dr. Robert Tamburro of the NICHD and Professor Alan Isles of the University of Queensland for review and advice concerning the article.

REFERENCES

1. Santschi M, Jouvet P, Leclerc F, et al; PALIVE Investigators; Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI); European Society of Pediatric and Neonatal Intensive Care (ESPNIC): Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med* 2010; 11:681–689
2. Khemani RG, Sward K, Morris A, et al; NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN): Variability in usual care mechanical ventilation for pediatric acute lung injury: The potential benefit of a lung protective computer protocol. *Intensive Care Med* 2011; 37:1840–1848
3. Brower RG, Matthay MA, Morris A, et al; Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared

with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308

4. Putensen C, Theuerkauf N, Zinserling J, et al: Meta-analysis: Ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med* 2009; 151:566–576
5. Villar J, Kacmarek RM, Pérez-Méndez L, et al: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. *Crit Care Med* 2006; 34:1311–1318
6. Rubenfeld GD, Cooper C, Carter G, et al: Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med* 2004; 32:1289–1293
7. Spragg RG, Bernard GR, Checkley W, et al: Beyond mortality: Future clinical research in acute lung injury. *Am J Respir Crit Care Med* 2010; 181:1121–1127
8. Curley MA, Hibberd PL, Fineman LD, et al: Effect of prone positioning on clinical outcomes in children with acute lung injury: A randomized controlled trial. *JAMA* 2005; 294:229–237
9. Curley MA, Wypij D, Watson RS, et al; RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators Network: Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. *JAMA* 2015; 313:379–389
10. Willson DF, Thomas NJ, Tamburro R, et al; Pediatric Acute Lung and Sepsis Investigators Network: Pediatric calfactant in acute respiratory distress syndrome trial. *Pediatr Crit Care Med* 2013; 14:657–665
11. Khemani RG, Newth CJ: The design of future pediatric mechanical ventilation trials for acute lung injury. *Am J Respir Crit Care Med* 2010; 182:1465–1474
12. Khemani R, Sward K, Newth CJ: Adaptation of an adult based mechanical ventilation protocol for application in pediatric ALI/ARDS. *Am J Respir Crit Care Med* 2010; 181:A3903
13. Angoulvant F, Llor J, Alberti C, et al: Inter-observer variability in chest radiograph reading for diagnosing acute lung injury in children. *Pediatr Pulmonol* 2008; 43:987–991
14. Grasso S, Mascia L, Del Turco M, et al: Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology* 2002; 96:795–802
15. Khemani RG, Thomas NJ, Venkatachalam V, et al; Pediatric Acute Lung Injury and Sepsis Network Investigators (PALISI): Comparison of Spo_2 to Pao_2 based markers of lung disease severity for children with acute lung injury. *Crit Care Med* 2012; 40:1309–1316
16. Fessler HE, Hager DN, Brower RG: Feasibility of very high-frequency ventilation in adults with acute respiratory distress syndrome. *Crit Care Med* 2008; 36:1043–1048
17. von Ungern-Sternberg BS, Trachsel D, Erb TO, et al: Forced expiratory flows and volumes in intubated and paralyzed infants and children: Normative data up to 5 years of age. *J Appl Physiol (1985)* 2009; 107:105–111
18. Gauld LM, Kappers J, Carlin JB, et al: Height prediction from ulna length. *Dev Med Child Neurol* 2004; 46:475–480
19. Khemani RG, Markovitz BP, Curley MAQ: Characteristics of children intubated and mechanically ventilated in 16 PICUs. *Chest* 2009; 136:765–771
20. Blagev DP, Hirshberg EL, Sward K, et al: The evolution of eProtocols that enable reproducible clinical research and care methods. *J Clin Monit Comput* 2012; 26:305–317
21. Morris AH, Hirshberg E, Sward KA: Computer protocols: How to implement. *Best Pract Res Clin Anaesthesiol* 2009; 23:51–67
22. Ross PA, Newth CJ, Leung D, et al: Obesity and mortality risk in critically ill children. *Pediatrics* 2016; 137:e20152035
23. Ward SL, Quinn CM, Valentine SL, et al: Poor adherence to lung-protective mechanical ventilation in pediatric acute respiratory distress syndrome. *Pediatr Crit Care Med* 2016; 17:917–923
24. Kim P, Salazar A, Ross PA, et al: Comparison of tidal volumes at the endotracheal tube and at the ventilator. *Pediatr Crit Care Med* 2015; 16:e324–e331
25. Emeriaud G, Newth CJ; Pediatric Acute Lung Injury Consensus Conference Group: Monitoring of children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015; 16(5 Suppl 1):S86–S101
26. de Jager P, Burgerhof JG, van Heerde M, et al: Tidal volume and mortality in mechanically ventilated children: A systematic review and meta-analysis of observational studies. *Crit Care Med* 2014; 42:2461–2472
27. Arnold JH, Anas NG, Luckett P, et al: High-frequency oscillatory ventilation in pediatric respiratory failure: A multicenter experience. *Crit Care Med* 2000; 28:3913–3919
28. Gupta P, Green JW, Tang X, et al: Comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *JAMA Pediatr* 2014; 168:243–249
29. Bateman ST, Borasino S, Asaro LA, et al; RESTORE Study Investigators: Early high-frequency oscillatory ventilation in pediatric acute respiratory failure. A propensity score analysis. *Am J Respir Crit Care Med* 2016; 193:495–503
30. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin Definition. *JAMA* 2012; 307:2526–2533
31. Erickson S, Khemani RG, Zimmerman JJ, et al: Pediatric Acute Respiratory Distress Syndrome: Consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015; 16:428–39
32. Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723
33. Khemani RG, Conti D, Alonzo TA, et al: Effect of tidal volume in children with acute hypoxemic respiratory failure. *Intensive Care Med* 2009; 35:1428–1437
34. Newth CJ, Stretton M, Deakers TW, et al: Assessment of pulmonary function in the early phase of ARDS in pediatric patients. *Pediatr Pulmonol* 1997; 23:169–175
35. Hammer J, Numa A, Newth CJ: Albuterol responsiveness in infants with respiratory failure caused by respiratory syncytial virus infection. *J Pediatr* 1995; 127:485–490