Adherence to Lung-Protective Ventilation Principles in Pediatric Acute Respiratory Distress Syndrome

Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) V.2. Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network; Bhalla, Anoopindar K; Klein, Margaret J; Emeriaud, Guillaume; Lopez-Fernandez, Yolanda M; Napolitano, Natalie; Fernandez, Analia; Al-Subu, Awni M; Gedeit, Rainer; Shein, Steven L

Published in:
Critical Care Medicine

DOI:
10.1097/CCM.0000000000005060

Adherence to Lung-Protective Ventilation Principles in Pediatric Acute Respiratory Distress Syndrome: A Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Study

OBJECTIVES: To describe mechanical ventilation management and factors associated with nonadherence to lung-protective ventilation principles in pediatric acute respiratory distress syndrome.

DESIGN: A planned ancillary study to a prospective international observational study. Mechanical ventilation management (every 6 hr measurements) during pediatric acute respiratory distress syndrome days 0–3 was described and compared with Pediatric Acute Lung Injury Consensus Conference tidal volume recommendations (< 7 mL/kg in children with impaired respiratory system compliance, < 9 mL/kg in all other children) and the Acute Respiratory Distress Syndrome Network lower positive end-expiratory pressure/higher Fio_2 grid recommendations.

SETTING: Seventy-one international PICUs.

PATIENTS: Children with pediatric acute respiratory distress syndrome.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Analyses included 422 children. On pediatric acute respiratory distress syndrome day 0, median tidal volume was 7.6 mL/kg (interquartile range, 6.3–8.9 mL/kg) and did not differ by pediatric acute respiratory distress syndrome severity. Plateau pressure was not recorded in 97% of measurements. Using delta pressure (peak inspiratory pressure – positive end-expiratory pressure), median tidal volume increased over quartiles of median delta pressure ($p = 0.007$). Median delta pressure was greater than or equal to 18 cm H_2O for all pediatric acute respiratory distress syndrome severity levels. In severe pediatric acute respiratory distress syndrome, tidal volume was greater than or equal to 7 mL/kg 62% of the time, and positive end-expiratory pressure was lower than recommended by the positive end-expiratory pressure/Fio_2 grid 70% of the time. In multivariable analysis, tidal volume nonadherence was more common with severe pediatric acute respiratory distress syndrome, fewer PICU admissions/yr, non-European PICUs, higher delta pressure, corticosteroid use, and pressure control mode. Adherence was associated with underweight stature and cuffed endotracheal tubes. In multivariable analysis, positive end-expiratory pressure/Fio_2 grid nonadherence was more common with higher pediatric acute respiratory distress syndrome severity, ventilator decisions made primarily by the attending physician, pre-ICU cardiopulmonary resuscitation, underweight stature, and age less than 2 years. Adherence was associated with respiratory

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DOI: 10.1097/CCM.0000000000005060

therapist involvement in ventilator management and longer time from pediatric acute respiratory distress syndrome diagnosis. Higher nonadherence to tidal volume and positive end-expiratory pressure recommendations were independently associated with higher mortality and longer duration of ventilation after adjustment for confounding variables. In stratified analyses, these associations were primarily influenced by children with severe pediatric acute respiratory distress syndrome.

CONCLUSIONS: Nonadherence to lung-protective ventilation principles is common in pediatric acute respiratory distress syndrome and may impact outcome. Modifiable factors exist that may improve adherence.

KEY WORDS: artificial; mortality; pediatrics; respiration; respiratory distress syndrome

Lung-protective ventilation prioritizing limiting tidal volume (V_T) and driving pressure (plateau pressure [Pplat]—positive end-expiratory pressure [PEEP]) and application of PEEP to maintain lung recruitment are evidence-based practices in acute respiratory distress syndrome (ARDS). Randomized controlled trials in adults with ARDS have confirmed that failure to adhere to these lung-protective principles results in higher mortality (1–4).

Randomized trials assessing lung-protective ventilation strategies in pediatric ARDS (PARDS) have not been performed, although the same principles were recommended by the Pediatric Acute Lung Injury Consensus Conference (PALICC) for ventilator management (5). Many of these recommendations are based on pediatric observational data, coupled with preclinical animal data and adult clinical trials. Randomized controlled trials in which children with PARDS are exposed to high V_T, high driving pressures, or low PEEP are considered almost unfeasible (6). In that context, it is essential to understand which recommendations for lung-protective ventilation are followed in PARDS, and whether failure to adhere to recommendations is associated with outcome.

As a planned ancillary to the PARDS Incidence and Epidemiology (PARDIE) study, we sought to describe the international practice of mechanical ventilation in PARDS and specifically evaluate the frequency with which management is consistent with lung-protective ventilation recommendations. We also sought to identify PICU, patient, and management characteristics associated with nonadherence with recommendations and if this nonadherence was associated with mortality or duration of ventilation.

MATERIALS AND METHODS

This was an ancillary study (V.2.) on respiratory support during PARDS to a prospective cross-sectional observational study (PARDIE, V.0.). PARDIE enrolled children with a new PARDS diagnosis over 10 distinct study weeks from international PICUs in 2016 and 2017 (7, 8). The PARDIE protocol was first approved by the Children's Hospital Los Angeles (CHLA) Institutional Review Board (IRB) (CHLA 16-00043), and sites either obtained local IRB approval or used the central CHLA IRB as previously published (8). All PARDIE sites but one were granted a waiver of informed consent. V.2. data submission was optional for each PICU. This analysis included children with V.2. data who received conventional ventilation during the study period. Children were excluded if all measurement time points had an endotracheal tube leak greater than 20% or an incalculable PARDS severity oxygen saturation [Spo_2] > 97% or missing data).

Our primary objective was to describe international PARDS conventional mechanical ventilation practice and to assess adherence to lung-protective ventilation recommendations. Secondary objectives included determining variables associated with nonadherence to recommendations and if nonadherence was associated with PICU mortality or duration of ventilation (modeled as rate of extubation, with the competing risk of death). We hypothesized that lung-protective ventilation recommendations are often not followed in PARDS and that nonadherence may contribute to higher mortality and longer duration of ventilation.

We evaluated the PALICC recommendation that V_T should be adjusted based on respiratory system compliance, with a lower V_T of 3–6 mL/kg predicted body weight (PBW) for children with impaired respiratory system compliance and V_T 5–8 mL/kg for all other children (5). PALICC recommends PEEP of greater than or equal to 10 cm H_2O for severe PARDS, but no specific recommendations are given for nonsevere PARDS. Hence, we evaluated PEEP management in relation to the ARDS Network (ARDSNet) lower PEEP/higher F_{IO_2} grid (PEEP/F_{IO_2} grid) (3). PALICC guidelines recommended limiting Pplat to decrease risk

of barotrauma as they were published prior to recent understanding of the importance of driving pressure (Pplat–PEEP). We sought to evaluate Pplat and driving pressure in this study. However, Pplat was rarely reported, so we instead evaluated delta pressure (peak inspiratory pressure [PIP]–PEEP) to assess risk for barotrauma.

Approximately every 6 hours during PARDS days 0–3, data on respiratory support were collected with supplementary data obtained from other PARDIE studies (**Supplemental Digital Content 1**, http://links.lww.com/CCM/G447) (8–11). Instructions were given to collect respiratory support data during steady state conditions. For each measurement time point, PARDS severity was classified as resolved (no longer meeting PARDS oxygenation criteria), mild, moderate, or severe using oxygenation cut points (**Supplemental Digital Content 2**, http://links.lww.com/CCM/G448) (12). PARDS severity of illness was determined using a previously published predictive model which adjusts for immunocompromised conditions, organ dysfunction, vasopressor-inotrope score, Pao_2/Fio_2 ratio, and fluid balance (9). A set PEEP that was lower than the recommended PEEP on the PEEP/Fio_2 grid for the set Fio_2 was classified as nonadherence.

PALICC V_T recommendations are based on respiratory system compliance (3–6 mL/kg if poor respiratory system compliance and 5–8 mL/kg in children with more preserved respiratory system compliance) (5). We were unable to calculate respiratory system compliance in most children because we could not guarantee the absence of respiratory effort and because Pplat was rarely measured. Therefore, we defined a V_T greater than or equal to 7 mL/kg as nonadherent for severe PARDS (i.e., oxygenation index ≥ 16 or oxygen saturation index ≥ 12.3), assuming poor respiratory system compliance in this subgroup, and V_T greater than or equal to 9 mL/kg was nonadherent in nonsevere PARDS. We calculated the percent of nonadherent V_T and PEEP/Fio_2 measurement time points per child (for children with ≥ 3 available measurement time points).

Analyses were performed with SAS (Version 9.4, SAS Institute, Cary, NY) and STATA 15 (StataCorp LLC, College Station, TX). Descriptive statistics were used to summarize ventilator management using daily medians for each child. Using multivariable mixed effects logistic regression modeling, we assessed variables that were independently associated with a nonadherent V_T or PEEP/Fio_2 combination. In a sensitivity analysis, we limited the nonadherent V_T analysis to the subgroup with a cuffed endotracheal tube. We constructed a mixed effects multivariable logistic regression model to determine the independent association between percent nonadherence (V_T, PEEP/Fio_2 grid) and mortality. A multivariable proportional hazards model for competing risks was used to assess the association between percent nonadherence (V_T, PEEP/Fio_2 grid) and rate of extubation at any given time after intubation with the competing risk of death. Variables found to be independently associated with nonadherence and the presence of a comorbid condition, PARDS severity of illness, use of high frequency oscillatory ventilation, and extracorporeal membrane oxygenation were considered as possible confounders in the models. Variables remained in the final multivariable model if they changed the effect estimate for either predictor variable by greater than 20%. Stratified analysis was performed by PARDS severity (severe vs nonsevere). See Supplemental Digital Content 2 (http://links.lww.com/CCM/G448) for additional details on the methods.

RESULTS

There were 422 children from 71 PICUs (32 North American, 17 European, 13 Central or South American, and 9 Asian, Australian, or New Zealand) included in the analyses (**Supplemental Digital Content 3**, http://links.lww.com/CCM/G449). The median age was 2.8 years (interquartile range [IQR], 0.7–9.4 yr), with 63% male (**Supplemental Digital Content 4**, http://links.lww.com/CCM/G450). There were 76 nonsurvivors (18%), and the median duration of ventilation for survivors was 6.2 days (IQR, 3.2–11.7 d).

Description of Conventional Mechanical Ventilation Management

The most common mode in the first 24 hours of PARDS was a pressure control mode (n = 142; 37.8%) followed by a pressure-regulated volume control or other related mode (n = 102; 27.1%) with pressure control being used more commonly as PARDS severity increased (**Supplemental Digital Content 5**, http://links.lww.com/CCM/G451). Pplat was reported in 2.9% of measurements. In the first 24 hours of PARDS, the median V_T was 7.6 mL/kg PBW (IQR, 6.3–8.9 mL/kg PBW) and

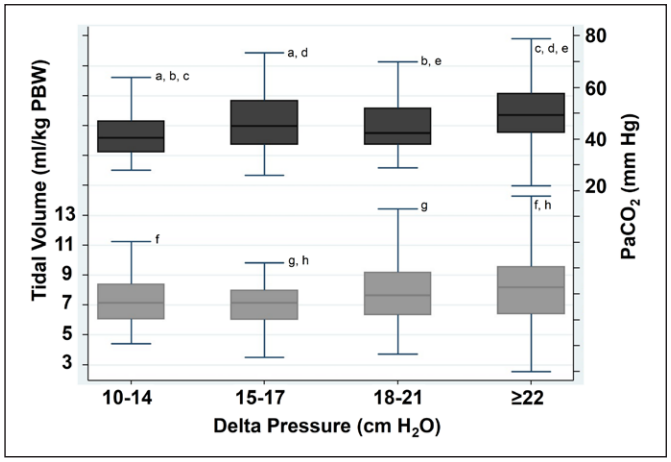

Figure 1. Median tidal volume (*light gray*) and $Paco_2$ (*dark gray*) in the first 24 hr of pediatric acute respiratory distress syndrome by delta pressure quartile. *Box* and *line* represent median, of the median values for each child, and interquartile range, *whiskers* represent upper and lower adjacent ranges. Median tidal volume increased over delta pressure quartiles ($p = 0.007$) as did median $Paco_2$ ($p = 0.0001$). Significant differences ($p < 0.05$) for comparisons between delta pressure quartiles are notated (a, b, c, etc.) (Dunn's test for multiple comparisons). There were 337 children with tidal volume and 272 children with $Paco_2$ data available for day 0. PBW = predicted body weight.

did not differ by PARDS severity ($p = 0.28$). Although the PALICC recommendation is to use lower V_T for those with more impaired respiratory system compliance, median V_T increased as median delta pressure increased (delta pressure 10–15 cm H_2O: V_T 7.1 mL/kg PBW [IQR, 6.1–8.4 mL/kg PBW], delta pressure 15–17 cm H_2O: V_T 7.1 mL/kg PBW [IQR, 6.0–8.0 mL/kg PBW], delta pressure 18–22 cm H_2O: V_T 7.6 mL/kg PBW [IQR, 6.4–9.2 mL/kg PBW], delta pressure ≥ 22 cm H_2O: V_T 8.2 mL/kg PBW [IQR, 6.4–9.6 mL/kg PBW]; $p = 0.007$) (**Fig. 1**). $Paco_2$ also increased with higher delta pressure ($p = 0.0001$). Median PIP, delta pressure, and PEEP increased as PARDS severity worsened (all $p < 0.0001$). Median delta pressure was greater than or equal to 18 cm H_2O for all severity levels. These findings were similar 24–48 hours and 48–72 hours after PARDS diagnosis (Supplemental Digital Content 5, http://links.lww.com/CCM/G451).

Adherence With PALICC V_T Recommendations

V_T was greater than or equal to 7 mL/kg PBW in 61.9% of severe PARDS measurements and greater than or equal to 9 mL/kg in 28.9% of nonsevere PARDS measurements. When examining V_T adherence by PICU, there were differences between regions and individual PICUs (**Supplemental Digital Content 6**, http://links.lww.com/CCM/G452).

Adherence with PEEP/Fio_2 Grid Recommendations

A lower PEEP than recommended by the ARDSNet lower PEEP/higher Fio_2 grid was used 70% of the time when children had severe PARDS and 71% of the time when Fio_2 greater than 0.5 (Supplemental Digital Content 5, http://links.lww.com/CCM/G451 and **Supplemental Digital Content 7**, http://links.lww.com/CCM/G453).

Variables Associated With Nonadherence

In multivariable analysis, variables associated with a V_T higher than recommended included having severe PARDS, fewer PICU admissions/yr, non-European PICUs, a pressure control mode, a higher delta pressure, and receiving corticosteroids (**Table 1**). Variables associated with V_T management in-line with recommendations included underweight stature and a cuffed endotracheal tube. In a sensitivity analysis limited to children with a cuffed endotracheal tube, these variables retained their associations (all $p < 0.03$).

In multivariable analysis, variables associated with a PEEP lower than recommended were PARDS severity (mild, moderate, severe vs resolved), ventilator decisions made primarily by the attending physician, receiving pre-ICU CPR, underweight stature, and age less than 2 years (vs age 2–8 yr) (**Table 2**). Respiratory therapist involvement in ventilator management and measurement time points greater than 48 hours from PARDS diagnosis (vs <24 hr) were associated with a PEEP at or above recommendations. There was a significant interaction between Fio_2 and Spo_2 with higher odds of PEEP lower than recommended with higher Fio_2 and lower Spo_2.

Nonadherence and Outcome

In multivariable logistic regression modeling, the percent of measurements with a V_T higher than recommended ($p = 0.011$) and PEEP lower than recommended ($p = 0.032$) in the first 72 hours of PARDS were both independently associated with a higher PICU mortality after adjustment for PARDS severity of illness and average PICU admissions/yr (**Table 3**).

TABLE 1.
Multivariable Mixed Effects Logistic Regression Model for Nonadherence With Tidal Volume Recommendations (367 Children, From 68 PICUs, with 3,340 Measurement Time Points)

Multivariable Model Variables	OR (95% CI)	*p*
Severe pediatric acute respiratory distress syndrome	25.59 (11.40–57.44)	< 0.0001
Region		
North America	10.59 (2.06–54.47)	0.005
Central and South America	33.63 (4.87–232.01)	0.0004
Middle East/Asia/Australia/New Zealand	17.12 (1.53–190.96)	0.021
Europe	Reference	NA
BMI, kg/m^2		
Underweight (BMI < 18.5)	0.31 (0.13–0.75)	0.009
Normal (BMI 18.5–24.9)	Reference	NA
Overweight (BMI 25–29.9)	4.99 (0.83–29.92)	0.08
Obese (BMI > 30)	7.18 (0.67–76.60)	0.10
Average PICU admissions, per year		
≤ 250	12.20 (1.12–133.22)	0.04
251–500	1.10 (0.12–10.56)	0.93
501–750	10.63 (2.18–51.76)	0.003
751–1,000	0.36 (0.08–1.59)	0.18
1,001–1,250	1.73 (0.40–7.53)	0.46
> 1,250	Reference	NA
Corticosteroids	2.93 (1.68–5.12)	0.0002
Delta pressure (per 1 cm H_2O increase)	1.04 (1.01–1.08)	0.02
Cuffed endotracheal tube	0.27 (0.08–0.93)	0.04
Pressure controlled mode of ventilation	1.79 (1.02–3.15)	0.04

BMI = body mass index, NA = not applicable, OR = odds ratio.
Overall nonadherence with tidal volume recommendations in this subgroup was 31.8%..

Delta pressure met criteria as a confounder; however, the model became unstable once it was added, suggesting multicollinearity, and it was removed. In stratified analysis based on PARDS severity, V_T higher than recommended remained independently associated with higher mortality (p = 0.002) for children with severe PARDS (at least 1 measurement time point of severe PARDS), with a trend for higher mortality for those with PEEP lower than recommended (p = 0.11) (**Supplemental Digital Content 8**, http://links.lww.com/CCM/G454). There was no association between adherence to V_T and PEEP recommendations and mortality in children with nonsevere PARDS (all $p > 0.3$).

In a multivariable competing risk regression model, the percent of V_T measurements above recommended (p = 0.023) and the percent of PEEP measurements below recommended (p = 0.01) were independently associated with a lower rate of extubation at any given time after

TABLE 2.

Multivariable Mixed Effects Logistic Regression Model for Positive End-Expiratory Pressure Nonadherence (385 Children, From 70 PICUs, With 3,856 Measurement Time Points)

Multivariable Model Variables	OR (95% CI)	*p*
PARDS severity		
Resolved	Reference	NA
Mild	2.28 (1.33–3.90)	0.003
Moderate	2.08 (1.04–4.16)	0.039
Severe	3.41 (1.36–8.56)	0.009
BMI, kg/m^2		
Underweight (BMI < 18.5)	2.17 (1.05–4.48)	0.036
Normal (BMI 18.5–24.9)	Reference	NA
Overweight (BMI 25–29.9)	0.38 (0.10–1.42)	0.15
Obese (BMI > 30)	0.52 (0.10–2.78)	0.48
Age, yr		
< 2	3.79 (1.66–8.68)	0.002
≥ 2–8	Reference	NA
≥ 8	1.36 (0.50–3.72)	0.55
Hours from PARDS diagnosis		
< 24	Reference	NA
≥ 24–48	0.74 (0.50–1.12)	0.15
≥ 48	0.47 (0.28–0.78)	0.004
Ventilator decisions made primarily by the attending physician	2.55 (1.23–5.30)	0.012
Respiratory therapist involved in ventilator management	0.25 (0.11–0.57)	0.0009
Pre-ICU cardiopulmonary resuscitation	7.57 (2.03–28.26)	0.003

BMI = body mass index, NA = not applicable, OR = odds ratio, PARDS = pediatric acute respiratory distress syndrome.
Overall nonadherence (management with a positive end-expiratory pressure [PEEP] lower than recommended by the Acute Respiratory Distress Syndrome Network lower PEEP/higher F_{IO_2} grid) in this subgroup was 28.7%. The final model is adjusted for F_{IO_2} and oxygen saturation at the time of the measurement and the interaction between the two variables.

intubation (longer duration of ventilation) after adjustment for PARDS severity of illness (**Table 4**). In stratified analyses based on PARDS severity, the percent of V_T measurements above recommended (p = 0.003) and PEEP measurements below recommended (p = 0.008) remained independently associated with a lower rate of extubation at any given time after intubation (longer duration of ventilation) in children with severe PARDS (Supplemental Digital Content 8, http://links.lww.com/CCM/G454). There was no association between adherence to V_T or PEEP recommendations and duration of ventilation in children with nonsevere PARDS (all p > 0.5).

TABLE 3.

The Association Between Ventilator Management in the First 72 Hours of Pediatric Acute Respiratory Distress Syndrome and PICU Mortality (337 Subjects From 63 PICUs)

Multivariable Model Variables	OR (95% CI)	*p*
Percent of nonadherent measurements (positive end-expiratory pressure/Fio_2 grid) (per 10% increase)	1.12 (1.01–1.23)	0.032
Percent of nonadherent measurements (tidal volume)		
0–33	Reference	NA
33–67	0.90 (0.33–2.42)	0.83
67–100	2.83 (1.27–6.33)	0.011
Average PICU admissions, per year		
≤ 250	0.66 (0.12–3.59)	0.63
251–500	0.19 (0.03–1.16)	0.07
501–750	0.56 (0.16–1.91)	0.36
751–1,000	1.50 (0.44–5.10)	0.51
1,001–1,250	2.12 (0.73–6.15)	0.17
> 1,250	Reference	NA
Pediatric acute respiratory distress syndrome severity of illness	2.47 (1.83–3.35)	< 0.0001

NA = not applicable.
This analysis is limited to subjects with more than three measurement time points on conventional ventilation in the first 72 hr of pediatric acute respiratory distress syndrome. There was a median of 12 measurement time points (interquartile range, 10–13) per subject in this analysis. Nonadherence with the positive end-expiratory pressure (PEEP)/Fio_2 grid was determined to be a PEEP lower than recommended for a given Fio_2. There were 218 children (64%) with 0–33% of nonadherent tidal volume measurements, 46 children (13.4%) with 33–67% of nonadherent tidal volume measurements, and 79 children (23%) with > 67% of nonadherent tidal volume measurements.

TABLE 4.

Multivariable Competing Risks Regression Model for Percent Nonadherence to Tidal Volume and Positive End-Expiratory Pressure Recommendations With Rate of Extubation at Any Given Time After Intubation (340 Subjects From 64 PICUs)

Multivariable Model Variables	SHR (95% CI)	*p*
Percent of nonadherent measurements (positive end-expiratory pressure/Fio_2 grid) (per 10% increase)	0.96 (0.93–0.99)	0.01
Percent of nonadherent measurements (tidal volume)		
0–33	Reference	Not applicable
33–67	0.95 (0.68–1.32)	0.74
67–100	0.73 (0.56–0.96)	0.023
Pediatric acute respiratory distress syndrome severity of illness	0.72 (0.65–0.79)	< 0.0001

SHR = subdistribution hazard ratio.
This analysis is limited to subjects with more than three measurement time points on conventional ventilation in the first 72 hr of pediatric acute respiratory distress syndrome. There was a median of 12 measurement time points (interquartile range, 10–13) per subject for the assessment of % adherence. Nonadherence with the positive end-expiratory pressure (PEEP)/Fio_2 grid was determined to be a PEEP lower than recommended for a given Fio_2.

DISCUSSION

This represents the largest international prospective study of mechanical ventilation management in PARDS demonstrating that nonadherence to lung-protective principles in PARDS is common. In particular, V_T is not lowered for those with severe PARDS or high delta pressure and does not vary by PARDS severity. We also found that use of V_T higher than recommended by the PALICC guidelines is independently associated with higher mortality and longer duration of mechanical ventilation. Furthermore, we have confirmed previous findings that use of PEEP levels lower than recommended by the ARDSNet lower PEEP/higher Fio_2 grid is independently associated with worse outcome. This lack of adherence and association with worse outcomes is largely driven by children with severe PARDS, highlighting that we may fail to use lung-protective principles in the children that need them most.

The idea that V_T should be patient specific and titrated based on lung compliance (or functional

residual capacity) underscores the physiologic concepts of lung strain and serves as the basis of the PALICC recommendations. However, we found that V_T management is often not patient specific in PARDS. V_T is not adjusted based on PARDS severity and is *higher* in children with higher delta pressure, presumably the children with lower respiratory system compliance. This is the first evidence that higher V_T in PARDS is associated with poor outcome; however, there are important limitations to this analysis. Pplat, required to calculate static respiratory system compliance and driving pressure (Pplat–PEEP), was rarely reported. Furthermore, many patients had spontaneous respiratory effort, which precludes accurate calculations of dynamic compliance. Therefore, we had no direct measure of respiratory system compliance to adjust for in multivariable modeling. Furthermore, in the multivariable models, we evaluated the percent of measurements which were adherent with V_T recommendations over the first 72 hours, rather than raw V_T, to capture the concept of patient specific V_T based on PARDS severity. But, this approach leaves the possibility that percent adherence identifies children with the phenotype of persistent severe PARDS. It is possible that rather than contributing to harm, higher V_T reflects higher patient severity not fully controlled for in our analysis. Previous observational studies in PARDS have not identified a relationship between V_T and mortality perhaps because they did not accept the a priori concept that the most severely lung injured patients should receive the smallest V_T (13, 14). Although our analysis suggests higher V_T may be associated with higher mortality, particularly in children with severe PARDS, this result should be interpreted with caution and requires study with more granular data.

Our previous multisite observational study on PEEP/F_{IO_2} management found that lower PEEP than the PEEP/F_{IO_2} grid recommended in the first 24 hours of PARDS was associated with higher mortality (15). Our results confirm and expand this finding to the first 72 hours of PARDS in an international cohort. Although there remains the possibility of residual confounding, our analysis supports that two components of management, V_T and PEEP, are both independently associated with mortality and duration of ventilation in children.

Driving pressure (Plat–PEEP) was not available for most patients in this dataset because Pplat was rarely reported. We believe this represents clinical practice, Pplat is not routinely measured, particularly for children on modes of ventilation with decelerating flow patterns (pressure control or pressure regulated). Delta pressure (PIP–PEEP) has limitations as it includes both resistive and elastic components; nonetheless, most children with PARDS do not have elevated airway resistance (16). Furthermore, if a child has respiratory effort, delta pressure may underestimate driving pressure. However, these factors would likely decrease the impact of pressure variables on the analysis which is why we assessed delta pressure. Across severity ranges, median delta pressure (PIP–PEEP) was consistently greater than or equal to 18 cm H_2O. Therefore, it is likely that driving pressure was higher than adult-based recommendations ($\geq$ 14 cm H_2O) for most children with PARDS. However, it remains to be determined whether driving pressure is more associated with clinical outcome than either V_T or PEEP management in children. At a minimum, these data highlight that pediatric intensivists do not measure driving pressure but certainly should.

It is important to try to understand barriers to implementation of lung-protective ventilation. We found lower PEEP levels were used than recommended in younger and underweight children. Although it is well-accepted that higher PEEP to counter the weight of the chest wall in obese patients is beneficial, whether underweight or young children (with more compliant chest walls) require less PEEP has not been studied (17, 18). The association between corticosteroid use and nonadherence to V_T recommendations is not clear. This may reflect clinician concern for lower airway obstruction (larger volume, lower rate ventilator management). To change pediatric ventilator management, these questions need to be studied, likely with more advanced respiratory monitoring (e.g. Pplat, transpulmonary pressures, static resistance and compliance measurements, and forced vital capacity curves).

Some PICUs were more adherent with V_T recommendations; processes in these units deserve further investigation. Children who were underweight were less likely to be managed with a high V_T, suggesting V_T is usually indexed to actual body weight, rather than PBW. It should be noted that there is no one accepted method internationally with which to determine PBW in children, and potentially, our method does not apply across an international cohort (19). Efforts to improve clinician

focus on exhaled V_T when using either an uncuffed endotracheal tube or a pressure control mode (nonvolume targeted) may also be important to improve adherence. Our findings suggest that instead of attending physicians primarily making ventilator decisions, collaborative ventilator management with respiratory therapists or use of computer decision support tools may also increase adherence and attention to following recommendations. Increasing adherence over time suggests efforts to improve adherence may require special focus on the initial stabilization of children with PARDS.

In adults with ARDS, the Large observational study to UNderstand the Global Impact of Severe Acute respiratory FailurE (LUNG SAFE) observational study also found poor adherence to lung-protective ventilation principles and limited reporting of Pplat measurements (20). In another study, greater than 90% of clinicians stated their ARDS patients would benefit from low V_T ventilation; however, in clinical practice, the same clinicians changed less than 10% of patients with high V_T to low V_T management (21). These findings suggest an urgent need for methods to improve bedside recognition and rectification of nonadherence to management guidelines. This may include computer decision support tools which, in some studies, have improved adherence to lung-protective principles (22–24). Methods such as Standardized Clinical Assessment and Management Plans, which use an iterative process to assess reasons for nonadherence and modify guidelines as pertinent to individual patient variation and clinician acumen, should also be explored (25).

In addition to possible residual confounding, there are other limitations to this study. We obtained data every 6 hours which may not fully capture minute-to-minute changes in ventilator settings. There are no specific recommendations to manage PEEP based on the PEEP/F_{IO_2} grid in children, and therefore, nonadherence to the grid may simply represent lack of familiarity. We did not have data on unit-level ventilator management protocols and therefore were unable to assess specific aspects of protocol guidance or if protocolized management increased adherence. We did not have Pplat to calculate driving pressure and chose to present descriptive data on delta pressure, so these data must be interpreted with caution, as previously described. There were some missing or inconsistent data despite multiple queries to participating sites. Data management was approached in a consistent manner jointly by two investigators (A.B., M.K.) to limit bias; however, the possibility of selection bias remains. This ancillary study enrolled a subgroup of the children enrolled in the V.0. study which may have also increased the risk of selection bias. Mortality was similar to the V.0. mortality (17%) and to the mortality in other recent PARDS observational studies (13–19%), suggesting this was an appropriately representative sample of children with PARDS (8, 15, 26, 27).

CONCLUSIONS

Nonadherence to lung-protective principles in PARDS is common and may be associated with higher mortality and longer duration of ventilation. There are potentially modifiable factors associated with nonadherence that should be investigated further for strategies to improve adherence to evolving PARDS mechanical ventilation recommendations.

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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/ccmjournal).

Supported, in part, by Southern California Clinical Translational Science Institute, Sainte Justine Children's Hospital, University of Montreal, Canada, Réseau en Santé Respiratoire du Fonds de Recherche Quebec-Santé, and Children's Hospital Los Angeles, Department of Anesthesiology and Critical Care Medicine.

Dr. Bhalla's institution received funding from the Sainte Justine Children's Hospital, University of Montreal; she received support for article research from the National Institutes of Health (NIH). Drs. Bhalla's and Khemani's institutions received funding from the Southern California Clinical Translational Science Institute. Dr. Emeriaud's institution received funding from Fonds de recherche du Québec Santé and MaquetI; he is leading a feasibility study of a new ventilator which is financially supported by Maquet Critical Care. Dr. Napolitano's institution received funding from Drager, VERO-BIOTECH, Philips/Respironics, Aerogen, Actuated Medical, and Smiths Medical. Dr. Fernandez received funding from the Sociedad Argentina de Terapia Intesiva. Dr. Baudin received speaking fees and nonfinancial support from Maquet Critical Care. Dr. Cheifetz received funding from Philips (medical advisor), Medtronic (medical advisor), Tim Peters and Co. (consultant), Up-to-Date, and NIH National Heart, Lung, and Blood Institute (research grant). Dr. Kneyber serves as a consultant for Vyaire. Dr. Newth received funding from Philips Research North America and Nihon Kohden Orange Med. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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