Ventilatory Support in Children With Pediatric Acute Respiratory Distress Syndrome: Proceedings From the Pediatric Acute Lung Injury Consensus Conference

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The Pediatric Acute Lung Injury Consensus Conference Group is listed in **Appendix 1**.

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Objective: To describe the recommendations of the Pediatric Acute Lung Injury Consensus Conference for mechanical ventilation management of pediatric patients with acute respiratory distress syndrome.

Design: Consensus Conference of experts in pediatric acute lung injury.

Methods: The Pediatric Acute Lung Injury Consensus Conference experts developed and voted on a total of 27 recommendations focused on the optimal mechanical ventilation approach of the patient with pediatric acute respiratory distress syndrome. Topics included ventilator mode, tidal volume delivery, inspiratory plateau pressure, high-frequency ventilation, cuffed endotracheal tubes, and gas exchange goals. When experimental data were lacking, a modified Delphi approach emphasizing the strong professional agreement was used.

Results: There were 17 recommendations with strong agreement and 10 recommendations with weak agreement. There were no recommendations with equipoise or disagreement. There was weak agreement on recommendations concerning approach to tidal volume and inspiratory pressure limitation (88% to 72% agreement, respectively), whereas strong agreement could be achieved for accepting permissive hypercapnia. Using positive end-expiratory pressure levels greater than 15 cm H_2O in severe pediatric acute respiratory distress syndrome, under the condition that the markers of oxygen delivery, respiratory system compliance, and hemodynamics are closely monitored as positive end-expiratory pressure is increased, is strongly recommended. The concept of exploring the effects of careful recruitment maneuvers during conventional ventilation met an agreement level of 88%, whereas the use of recruitment maneuvers during

rescue high-frequency oscillatory ventilation is highly recommended (strong agreement).

Conclusions: The Consensus Conference developed pediatric-specific recommendations regarding mechanical ventilation of the patient with pediatric acute respiratory distress syndrome as well as future research priorities. These recommendations are intended to initiate discussion regarding optimal mechanical ventilation management for children with pediatric acute respiratory distress syndrome and identify areas of controversy requiring further investigation. (*Pediatr Crit Care Med* 2015; 16:S51–S60)

Key Words: lung injury; mechanical ventilation; pediatric acute respiratory distress syndrome

Mechanical ventilation can be indispensable for assuring adequate gas exchange for patients with acute respiratory failure. However, it may exacerbate, or even initiate, lung injury and inflammation and has, therefore, been identified as a risk factor for poor patient outcome. The development of ventilator-induced lung injury (VILI) has led to the concept of lung-protective ventilation strategies. Such an approach is based on two primary principles. The first is to avoid overdistension (i.e., volutrauma) and the other is to avoid or minimize the cyclic opening and closing of alveoli (i.e., atelectrauma) (1).

Ventilatory strategies that limit tidal stretch of the alveoli (e.g., low tidal volume ventilation and high-frequency ventilation), permissive gas exchange strategies (e.g., permissive hypercapnia and permissive hypoxemia), positive end-expiratory pressure (PEEP) titration with or without recruitment maneuvers, and ventilatory modes that partially or proportionally assist spontaneous breathing have been advocated. Unfortunately, specific pediatric outcome data on lung-protective ventilation are sparse, especially with regard to the ventilator strategy and/or mode(s) used to manage patients with pediatric acute respiratory distress syndrome (PARDS). There is generally a low level of evidence for most of the recommendations described in this article, and thus, specific recommendations are largely based on the experience in the adult population for patients with acute respiratory distress syndrome (ARDS), with consensus-based modifications for pediatrics.

MODES OF CONVENTIONAL VENTILATION

Recommendations:

3.1.1 There are no outcome data on the influence of mode (control or assisted) during conventional mechanical ventilation. Therefore, no recommendation can be made on the ventilator mode to be used in patients with PARDS. Future clinical studies should be designed to assess the control and assisted modes of ventilation on outcome. *Strong agreement*

Rationale

Controlled Versus Assisted Modes. Ventilator-delivered breaths can be either imposed on the patient independent of his/her own respiratory activity (i.e., nonsynchronized intermittent mechanical ventilation [IMV]) or used to partially (i.e., synchronized IMV [SIMV]) or fully (i.e., assist control, pressure control, or pressure support ventilation [PSV]) assist a patient's own respiratory effort. Each ventilator-assisted breath is defined by its cycle (i.e., transition from inspiration to expiration), trigger (i.e., initiation of inspiration), limit (i.e., size of the breath—pressure or volume), and inspiratory flow pattern (i.e., variable, decelerating or square-wave, constant).

Breath Cycling. Breath cycling (transition from inspiration to exhalation) can be determined by a clinician-set inspiratory time or by the patient based on the rate of inspiratory flow decay (i.e., flow termination criteria). Time-cycled breaths are typified by mechanical breaths, such as pressure-controlled or volume-controlled breaths. Flow-cycled breaths are typified by pressure support and volume support modes.

Breath Triggering. Traditionally, a ventilator breath is triggered by volume, flow, or pressure. In patients without adequate spontaneous effort, inspiration has to be triggered by time, that is, the respiratory rate setting. In spontaneously breathing patients, a ventilator-assisted breath is generally triggered by changes in flow in the ventilator circuit. Alternatively, variations in the pressure signal can be used and are especially favored for noninvasive ventilation or invasive ventilation with a significant air leak around the endotracheal tube (ETT).

Although trigger and cycling systems have technically been brought to high performance, especially for mechanical ventilators designed for the neonatal and/or pediatric patient population (2), there is no solid published experience in the pediatric population documenting that breath synchronization improves outcome (i.e., time on mechanical ventilation, duration of weaning, time spent in the PICU, or mortality) in patients with respiratory failure (3, 4). Similarly, in the neonatal setting, patient-ventilator synchronization has not shown improvement in outcome or long-term efficacy when compared with nonsynchronized ventilation (5).

Novel modes of ventilation have been developed with alternative triggers. The most common of these approaches is neurally adjusted ventilatory assist (NAVA) that uses the electrical activity signal of the diaphragm to trigger inspiration. This mode has been shown to improve patient-ventilator synchrony when compared with PSV in invasively (6–9) and noninvasively (10) ventilated patients. Furthermore, NAVA has shown in comparison with PSV in adult patients recovering from ARDS to not only improve patient-ventilator synchrony but also limit the risk of ventilator overassistance (11). Although NAVA has been shown in a nested study to reduce the duration of respiratory support for infants recovering from ARDS (12), it has not been demonstrated to improve overall outcome in any population studied.

Bilevel Ventilation With Spontaneous Breathing Throughout the Respiratory Cycle. Airway pressure release ventilation (APRV) is a mode of ventilation that allows for spontaneous breathing throughout all phases of the machine-imposed respiratory cycle. APRV is a pressure-limited, time-triggered, and time-cycled mode that maintains an elevated baseline pressure (P_{hi}) with deflations or "releases" of gas to

a lower pressure setting (P_{low}). With this mode of ventilation, adult experience has shown the possibility of using lower inspiratory plateau pressures for a given tidal volume when compared with volume ventilation as well as decreased sedation requirements (13).

Two randomized controlled trials (RCTs) have explored the use of APRV on outcomes in adult patients with ARDS. The first trial showed a significantly shorter duration of ventilation and ICU stay; however, it must be recognized that the control group of patients received neuromuscular blockade for unclear reasons for the first 3 days of ventilation. These results in favor of APRV, therefore, have to be questioned (14). The second RCT assigned 58 patients to either APRV or SIMV plus 10 cm H_2O of pressure support. This study demonstrated no differences in gas exchange, sedation requirements, or outcome (ventilator-free days or mortality) (15). Pediatric experience is limited to the results of one clinical trial. This prospective randomized crossover clinical trial compared APRV with volume-controlled synchronized IMV in children with mild-to-moderate lung injury (16). This study showed that APRV resulted in comparable levels of ventilation and oxygenation at significantly lower peak pressures.

Ventilator Mode and Outcome. Unfortunately, none of the various modes of ventilation has been demonstrated to improve the outcome in the pediatric population, including the patients with PARDS. From the adult experience, observational data have suggested that a high incidence of patient-ventilator asynchrony is related to increased morbidity (e.g., length on mechanical ventilation) in patients with ARDS, whereas a low incidence was associated with lower morbidity (17).

VENTILATORY STRATEGIES DURING CONVENTIONAL VENTILATION

Tidal Volume Delivery

Recommendations:

3.2.1 In any mechanically ventilated pediatric patient, we recommend in controlled ventilation to use tidal volumes in or below the range of physiologic tidal volumes for age/body weight (i.e., 5 to 8 mL/kg predicted body weight [PBW) according to lung pathology and respiratory system compliance. *Weak agreement (88% agreement)*

3.2.2 We recommend to use patient-specific tidal volumes according to disease severity. Tidal volumes should be 3–6 mL/kg PBW for patients with poor respiratory system compliance and closer to the physiologic range (5–8 mL/kg ideal body weight) for patients with better preserved respiratory system compliance. *Weak agreement (84% agreement)*

Rationale. In adult patients with ARDS, a large RCT comparing 6 versus 12 mL/kg of tidal volume showed a significantly lower mortality for the 6 mL/kg tidal volume group with a relative risk reduction of 24% and an absolute risk reduction of 9% (18). From subsequent meta-analyses, including four other studies comparing either small versus large tidal volume ventilation or pressure limitation at higher versus lower airway pressures, it was concluded that a V_t less than or equal to 10 mL/kg PBW (19, 20) is associated with improved survival. It is important to note that no pediatric or neonatal RCT has adequately studied the effects of small tidal volume ventilation or pressure limitation as a lung-protective ventilation strategy on outcome. However, it must be noted that two observational studies (one prospective and another retrospective in design) have shown an inverse relationship between applied tidal volumes and mortality in children (21, 22). Furthermore, a large retrospective multicenter analysis of patients with acute hypoxic respiratory failure (n = 439), of whom 345 (78.6%) developed ARDS according to the American-European Consensus definitions, did not show an association between tidal volume (even when tidal volumes < 6 mL/kg or > 10 mL/kg PBW were used) and mortality or ventilator-free days (23).

When considering small tidal volume ventilation as a lung-protective concept, it must be noted that physiologic tidal volumes in a normal person are in the range of 6–8 mL/kg PBW (24–29). When considering these clinical data in composite, tidal volumes above the physiologic range do not seem reasonable for any mechanically ventilated pediatric patients regardless of lung condition.

Patients with more severe lung injury, as expressed by poorer oxygenation, lower compliance (i.e., reflecting a small residual inflatable lung volume available for alveolar ventilation and gas exchange—"baby lung" concept) (30, 31), and a higher lung injury score by Murray et al (32) should receive tidal volumes below physiologic values. A subgroup analysis from the Acute Respiratory Distress Syndrome (ARDS) Network trial (18) in adult patients with ARDS (6 vs 12 mL/kg) compared patients with low versus high respiratory system compliance (using a compliance of 0.6 mL/cm H_2O/kg as a cutoff point) showed that only patients with poor respiratory system compliance at study entry had a survival benefit when randomized to the 6-mL/kg study arm (33). Similarly, there are appealing data from pediatric experience showing an inverse relationship to outcome with tidal volumes but a direct relationship with maximal airway pressures (21). This observation suggests strongly that clinicians tend to use lower V_t resulting in relatively higher inspiratory airway pressures in the sicker patients (i.e., patients with lower respiratory system compliance) at the onset of mechanical ventilation for ARDS. This latter observation is in alignment with data from the other pediatric observational study (22), showing that patients with higher initial lung injury scores were ventilated with smaller tidal volumes and showed worse outcome. These findings are consistent with the recent concept of keeping lung tissue strain (i.e., ratio between inflated volume and functional residual capacity) low to protect the lung (34).

Thus, the clinical observations from adult and pediatric ventilation studies would strongly suggest that targeting a V_t of 6 mL/kg PBW for every patient with ARDS, as would strongly be suggested by the results of the ARDS Network trial (18), may not be appropriate when reasoning on individual patient- and disease-specific pathophysiologic conditions. Interpretation of the available data suggests that each patient has a maximal allowable tidal volume that could avoid unacceptable high lung tissue strain. This thought process leads to the conclusion that

V_t should be adapted not only per patient body weight (mL/kg) but also on the amount of inflatable lung volume above functional residual capacity (i.e., V_t/baby lung/kg, or V_t/specific compliance/kg).

Various methods, most of them based on gender and height measures, have been proposed for estimating the body weight of infants and children in emergency settings when determining appropriate drug dosing (35–38), whereas for lung function measurements, it has been suggested that PBW should be calculated by using gender and height prediction from ulna length (39). This later method was developed to accurately predict the degree of restrictive lung pathologies in patients presenting with scoliosis and other syndromes associated with skeletal anomalies. For the purpose of estimating PBW in the ventilated child in the PICU setting, classical growth charts may allow reasonably accurate estimations for ventilation purposes by using gender, length/height, and head circumference.

Inspiratory Pressure

Recommendation:

3.2.3 In the absence of transpulmonary pressure measurements, we recommend an inspiratory plateau pressure limit of 28 cm H_2O, allowing for slightly higher plateau pressures (29–32 cm H_2O) for patients with increased chest wall elastance (i.e., reduced chest wall compliance). *Weak agreement (72% agreement)*

Rationale. Inspiratory pressure is a result of applied PEEP and the added volume of gas delivered above this pressure value. In a pressure-limited mode, peak inspiratory pressure (PIP) is defined by the change in pressure above the PEEP setting (Δ-P). In volume-limited ventilation, the PIP is defined by the V_t chosen and the pressure required above PEEP. Volutrauma (i.e., excessive volume delivery) by overdistension of lung units has been recognized to be a more injurious mechanism than barotrauma (i.e., excessive airway pressure) (1). However, limiting maximal inspiratory pressure is commonly proposed. It should be noted that the recommended pressure limitations often do not consider differences in chest wall elastance between patients of different body habitus or variations of elastance in the evolution of the disease process. To take these latter variables in account, one would need to measure transpulmonary pressures in every ventilated patient (40).

Because airway pressures are related to delivered V_t and respiratory system compliance, pressure limitation will result in a smaller V_t in conditions of lower compliance and in a larger V_t in more compliant lung conditions. As such, pressure limitation allows to some degree the "automatic" adaptation of the delivered tidal volume and, therefore, adjusts lung tissue strain to the actual pulmonary condition. As pressure-limited ventilation adjusts tidal volume based on the actual lung compliance and amount of residual inflatable lung volume in a sick lung, it can be recommended as a lung-protective strategy. However, in patients with severe reduced chest wall compliance (e.g., chest wall edema or obesity) or severely increased abdominal pressures, pressure limitation to pressure ranges of 25–28 cm H_2O may result in overly low transpulmonary pressures and, therefore, not allow sufficient inflation of the lungs to assure adequate alveolar ventilation and oxygenation.

Of importance, high inspiratory airway pressures have been associated in two observational pediatric studies with increased mortality (21, 22). One of these clinical reports demonstrates a clear and almost linear increase in adverse outcome with PIP greater than 25 cm H_2O (21).

Positive End-Expiratory Pressure

Recommendations:

3.3.1 We recommend moderately elevated levels of PEEP (10–15 cm H_2O) titrated to the observed oxygenation and hemodynamic response in patients with severe PARDS. *Weak agreement (88% agreement)*

3.3.2 We recommend that PEEP levels greater than 15 cm H_2O may be needed for severe PARDS although attention should be paid to limiting the plateau pressure as previously described. *Strong agreement*

3.3.3 We recommend that markers of oxygen delivery, respiratory system compliance, and hemodynamics should be closely monitored as PEEP is increased. *Strong agreement*

3.3.4 We recommend that clinical trials should be designed to assess the effects of elevated PEEP on outcome in the pediatric population. *Strong agreement*

Rationale. Levels of PEEP should be set to prevent lung unit collapse at end-expiration and avoid tidal recruitment at each breath cycle (collapse—opening—recollapse injury or so called atelectatic injury). This concept has been addressed in several experimental studies (41, 42) but not adequately in the clinical setting. Three randomized trials (43–45) in adult ARDS addressed higher versus lower levels of PEEP according various PEEP/F_{IO_2} tables but did not analyze PEEP in relation to collapse during end-expiration. None of these clinical investigations could demonstrate a difference in any outcome parameter. However, two systematic meta-analyses suggest that higher levels of PEEP as part of a lung-protective strategy may be associated with lower hospital mortality in adult patients with ARDS as defined by a ratio of partial pressure of oxygen to fraction of inspired oxygen concentration (Pa_{O_2}/F_{IO_2}) of 200 mm Hg or less (46, 47). However, this positive effect of PEEP was not seen in patients with milder forms of acute lung injury.

Lung Recruitment Maneuvers

Recommendations:

3.3.5 We recommend careful recruitment maneuvers in the attempt to improve severe oxygenation failure by slow incremental and decremental PEEP steps. Sustained inflation maneuvers cannot be recommended due to lack of available data. *Weak agreement (88% agreement)*

3.3.6 We recommend that clinical trials should be designed to assess optimal recruitment strategies in infants and children with PARDS. *Strong agreement*

Rationale. With the advent of small tidal volume ventilation, lung recruitment has gained new interest in patients with acute hypoxic respiratory failure with elevated requirements

for inspired oxygen concentrations. However, it has been recognized that recruitability of a diseased lung depends on various factors. Among others, it is dependent on the type of lung disease (e.g., diffuse alveolar disease vs pneumonia-like alveolar consolidations), time course (e.g., early vs late PARDS), and mechanics of the respiratory system (e.g., pulmonary compliance). In general, patients with predominantly increased lung elastance (i.e., decreased lung compliance) show less positive response to recruitment maneuvers than patients with increased chest wall elastance (i.e., decreased chest wall compliance) (48). However, lung pathology characterized predominantly by alveolar collapse (e.g., infant respiratory distress syndrome) or by inflammatory edema demonstrates a high potential for lung recruitment, despite being characterized mechanically by a low lung compliance. Similarly, application of a recruitment maneuver can improve oxygenation in adult patients with early ARDS (predominant inflammatory edema) who do not have impairment of chest wall mechanics (49).

Significant controversy exists on how to best apply recruitment maneuvers in clinical practice. Sigh maneuvers by increasing airway pressures to a level of 30–40 cm H_2O (or even higher) over a short period of time (generally 30–40 s) have shown variable results because their efficiency depends on the type of lung disease and respiratory system mechanics. Adult patients presenting with ARDS with high lung elastance (i.e., low lung compliance) and a primary ARDS etiology did not respond with improvement in oxygenation with such maneuvers to the degree that patients with low lung elastance due to a secondary ARDS did (49). In summary, patients with predominant lung unit collapse or inflammatory edema formation (e.g., early PARDS, infant respiratory distress syndrome, or similar pathologies) usually respond well to such recruitment maneuvers, especially if due to a secondary PARDS etiology.

Because it is often impossible to predict how an individual patient will respond to a lung recruitment attempt, careful individual PEEP titration seems to be a reasonable approach and has been shown to be efficient in terms of improvement of oxygenation and safe in adults and children with PARDS (50, 51).

A decremental PEEP titration trial has repeatedly been shown to be an efficient and safe method to determine a patient's optimal PEEP setting; however, recruitment and oxygenation have not yet been demonstrated to be determinants of clinically relevant outcomes (52, 53). No data exist on the effect of recruitment maneuvers on mortality, morbidity, length of stay, or duration of mechanical ventilation (54).

VENTILATORY STRATEGIES DURING "NONCONVENTIONAL" MECHANICAL VENTILATION

The term "nonconventional" mechanical ventilation is commonly used for ventilator modes that do not rely on convective gas exchange, the latter requiring tidal volumes above anatomical and apparatus dead space volumes. The respective modes are various types of high-frequency ventilation (e.g., high-frequency oscillatory ventilation [HFOV], high-frequency jet ventilation [HFJV], and high-frequency percussive ventilation [HFPV]) and tracheal gas insufflation. High-frequency ventilation is defined by a high-frequency rate (> 120 bpm for adults and > 150 bpm for infants and children) and a delivered tidal volume that is less than anatomic dead space.

High-Frequency Oscillatory Ventilation

Recommendations:

3.4.1 We recommend that HFOV should be considered as an alternative ventilatory mode in hypoxic respiratory failure in patients in whom plateau airway pressures exceed 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance. Such an approach should be considered for those patients with moderate-to-severe PARDS. *Weak agreement (92% agreement)*

3.4.2 In HFOV, we recommend that the optimal lung volume be achieved by exploration of the potential for lung recruitment by a stepwise increase and decrease of the mean airway pressure (continuous distending pressure) under continuous monitoring of the oxygenation and CO_2 response as well as hemodynamic parameters. *Strong agreement*

Rationale. Despite extensive experience with HFOV and multiple RCTs for neonatal respiratory failure, the use of HFOV as an elective or rescue ventilator mode for PARDS has not been studied extensively in children in the low tidal volume ventilation era.

The initial prospective study by Arnold et al (55) demonstrated that HFOV, using a high mean lung volume strategy, was safe in pediatric patients with respiratory failure and a high predicted mortality rate. In a post hoc analysis of retrospectively and prospectively collected data of 12 children (4 mo to 15 yr old) with acute severe respiratory failure refractory to conventional ventilation strategies, high-frequency ventilation was noted to improve gas exchange supporting the concept of HFOV as a rescue ventilatory mode (56).

The first RCT comparing HFOV to conventional mechanical ventilation studied 70 children with diffuse alveolar disease and/or airleak syndrome showed that HFOV resulted in a significant improvement in oxygenation and a decreased requirement for supplemental oxygen at 30 days by using an aggressive volume recruitment strategy. However, 30-day mortality was not changed. It should be noted that the control group in this study used a high delivered tidal volume in comparison with today's general management approach (57). A second RCT enrolling 61 patients (children > 35 kg and adults) with ARDS compared HFOV ($n = 37$) with conventional mechanical ventilation (CMV) ($n = 24$) showed no statistically significant differences in survival without chronic respiratory support, mortality, therapy failure, or crossover days (58).

Combined pediatric and adult experience with HFOV in ARDS was until recently promising for ARDS treatment showing a risk reduction (risk ratio, 0.77; 95% CI, 0.61–0.98) for the outcome parameter "hospital or 30-day mortality" as documented in a meta-analysis of six RCTs involving a total of 365 patients, most of them adults (59). This view has changed with the results of two recent large randomized studies, OSCillation in ARDS (60) and OSCILLATE (61), in which the adult patients with a Pa_{O_2}/F_{IO_2} less than 200 (i.e., moderate-to-severe ARDS) were randomized to HFOV or CMV. The OSCAR trial

showed no difference in outcome (30-day mortality), whereas the OSCILLATE trial was prematurely stopped (after the 500 patient analyses) by the steering committee because of a significantly higher in-hospital (47% vs 35%) and 60-day mortality (47% vs 38%) in the HFOV group. The results of the OSCAR and OSCILLATE studies can be partially explained by the observation that lung-protective ventilation strategies were applied in the CMV arm. Furthermore, concern has been raised about the OSCILLATE study given the number of patients in the HFOV group who required high vasopressor support because of hemodynamic compromise, suggesting the use of excessively high mean airway pressures and/or patients who were intravascularly deplete (e.g., shock) (62).

Similar to the OSCILLATE study, in a retrospective observational study by using the Virtual PICU System database, Gupta et al (63) concluded that HFOV had worse outcome when compared with conventional ventilation in children with acute respiratory failure. However, it must be noted that in addition to the limitations of a retrospective database analysis, the propensity scoring approach used in this study did not include clinically significant variables, such as airway pressures, fraction of inspired oxygen, and parameters of gas exchange (64).

Similarly, meta-analysis of neonatal RCTs comparing HFOV with CMV demonstrated that when both ventilatory modes were applied with a similar open lung-protective strategy, no difference existed in measured outcomes (65). However, from neonatal experience, it is strongly advocated to explore the volume-pressure (i.e., oxygenation-pressure) relationship during HFOV to maintain the oscillatory cycle on the deflation limb at an optimal open lung volume (i.e., open the lung at the lowest pressure required) (66). This approach has proven to be safe, but there are no outcome data with this technique. However, a recent relatively small RCT in neonates less than 28-week gestational age presenting with infant respiratory distress syndrome showed a reduction in time on the ventilator with HFOV at optimal lung volumes when compared with conventional mechanical ventilation at optimal lung volumes (i.e., after an lung recruitment attempt and determining the lowest airway pressure needed to maintain the lung open (67). This appears to be the first clinical trial comparing HFOV versus CMV that vigorously controlled for the applied ventilator strategy in both study arms.

In summary, data from pediatric and adult patients with diffuse alveolar disease and ARDS have demonstrated the safety of HFOV as well as improvements in short-term physiologic endpoints. However, it should be noted that the use of HFOV in the pediatric and adult populations has not yet been associated with significant improvements in clinically meaningful outcome measures. HFOV, although seemingly simple and straightforward in its application, requires multidisciplinary expertise to use, as is true of any mode of mechanical ventilation, and expertise with HFOV use was missing in many of the randomized controlled studies to date. Until more definitive data are obtained, it would seem reasonable to continue to include HFOV in the ventilatory armamentarium for the management of pediatric ARDS.

High-Frequency Jet Ventilation

Recommendations:

3.4.3 We cannot recommend the routine use of HFJV in children with PARDS. *Strong agreement*

3.4.4 We recommend that, in addition to the use of HFOV, HFJV might be considered in patients with severe air leak syndrome. *Weak agreement (64% agreement)*

Rationale. Evidence from a small RCT in adult patients demonstrates that ventilation and oxygenation can be achieved at lower peak airway pressures and tidal volumes with HFJV when compared with conventional ventilation (68). HFJV has certainly found its place as a ventilatory mode during laryngotracheal surgery. HFJV in PARDS has been reported only in a small series (29 children with severe ARDS complicated by pulmonary barotraumas) showing a survival rate of 69%. The authors speculated that the application of HFJV early in the course of severe hypoxemic respiratory failure complicated by airleak does allow for reduced airway pressures, thereby minimizing pulmonary barotrauma, and allowing the lung to recover from the underlying insult (69).

High-Frequency Percussive Ventilation

Recommendations:

3.4.5 HFPV is not recommended for routine ventilatory management of PARDS. *Strong agreement*

3.4.6 We recommend that HFPV can be considered in patients with PARDS and secretion-induced lung collapse, which cannot be resolved with routine clinical care (e.g., inhalational injuries). *Weak agreement (72% agreement)*

Rationale. HFPV is a lung-protective modality with the distinct advantage of improved secretion clearance, especially in those patients with burn injuries (70). Extrapolating the experience in these patients, HFPV has been extended to other populations of critically ill patients, including those with acute hypoxic respiratory failure (71, 72).

Liquid Ventilation

Recommendation:

3.5.1 The clinical use of liquid ventilation cannot be recommended. *Strong agreement*

Rationale. Although partial liquid ventilation (PLV) has been deemed a promising novel strategy for patients with acute hypoxemic respiratory failure, no study has demonstrated its efficacy. A recent Cochrane Review concluded that no evidence supports the use of PLV in ARDS, and some evidence suggests an increased risk of adverse events associated with its use (73).

Endotracheal Tubes

Recommendations:

3.6.1 Cuffed ETTs are recommended when conventionally ventilating a patient with PARDS. *Strong agreement*

3.6.2 We recommend allowing for an ETT air leak during HFOV to augment ventilation, if needed, assuming mean airway pressure can be maintained. *Strong agreement*

Rationale. Although there are no large-scale clinical trials that address cuffed versus uncuffed ETTs, there is a growing

body of suggestive literature that cuffed tubes are safe and may limit the need for repeat airway manipulations (74, 75). The use of cuffed ETTs may have the most benefit in those conditions with poor pulmonary compliance (i.e., those patients whose airleak may become excessive as pulmonary compliance worsens).

During HFOV, maintaining an ETT air leak may help to improve CO_2 washout, according to the principle of tracheal insufflations methods, and, therefore, such an approach can be recommended. However, leaks around the tube may reduce the effective distending pressure and lung-delivered oscillation volumes (76), for which the operator may need to compensate by increasing the mean airway pressure and amplitude settings.

GAS EXCHANGE

Oxygenation

Recommendations:

3.7.1 We recommend that oxygenation and ventilation goals be titrated based on the "perceived" risks of the toxicity of the ventilatory support required. *Strong agreement*

3.7.2 We recommend that, for mild PARDS with PEEP less than 10 cm H_2O, Spo_2 should generally be maintained at 92–97%. *Weak agreement (92% agreement)*

3.7.3 We recommend that, after optimizing PEEP, lower Spo_2 levels (in the range of 88–92%) should be considered for those with PARDS with PEEP greater than or equal to 10 cm H_2O. *Strong agreement*

3.7.4 Insufficient data exist to recommend a lower Spo_2 limit. *Strong agreement*

3.7.5 When Spo_2 is less than 92%, monitoring of central venous saturation and markers of oxygen delivery is recommended. *Strong agreement*

Rationale. In patients with ARDS, improved oxygenation has not been correlated with improved clinical outcomes (18, 77, 78). In the landmark ARDS Network low tidal volume study, the findings of improved mortality in the low tidal volume group of 6 mL/kg was not associated with improved oxygenation (18). Indeed, this study demonstrated that maximizing oxygenation may require increased ventilatory support, which resulted in worse outcome.

The concept of accepting lower arterial oxygenation saturation is termed "permissive hypoxemia" (79, 80). Although the acceptable arterial oxygen saturation target remains controversial, ventilatory strategies should aim to provide adequate tissue and organ oxygenation, while minimizing oxygen toxicity and VILI. Because the long-term neurologic and other end-organ (e.g., renal) effects of permissive hypoxemia have not been studied, clinicians must weigh the potential benefits and risks of this approach for each individual clinical situation.

Ventilation

Recommendations:

3.7.6 We recommend that permissive hypercapnia should be considered for moderate-to-severe PARDS to minimize VILI. *Strong agreement*

3.7.7 We recommend maintaining pH 7.15–7.30 within lung-protective strategy guidelines as previously described. There are insufficient data to recommend a lower limit for pH. Exceptions to permissive hypercapnia should include intracranial hypertension, severe pulmonary hypertension, select congenital heart disease lesions, hemodynamic instability, and significant ventricular dysfunction. *Weak agreement (92% agreement)*

3.7.8 Bicarbonate supplementation is not routinely recommended. *Strong agreement*

Rationale. By reducing minute ventilation, low tidal volume ventilation physiologically leads to hypercapnia. Although the exact degree of respiratory acidosis that can be tolerated is controversial, most undesirable effects are reversible and minor when the pH is greater than approximately 7.20, although the lower limit of acceptable pH is similarly debated (81). The medical literature suggests that low tidal volume pressure-limited ventilation with permissive hypercapnia may improve outcome in patients with ARDS (82, 83) Laboratory data from an ischemia-reperfusion acute lung injury model indicate that hypercapnic acidosis is protective and that buffering of the hypercapnic acidosis attenuates its protective effects (84). Permissive hypercapnia, however, is not applicable to all patient groups. Generally, this strategy should be avoided in patients with intracranial hypertension, severe pulmonary hypertension, select congenital heart disease lesions, hemodynamic instability, and significant ventricular dysfunction.

SUMMARY

Unfortunately, it must be recognized that clinical evidence for the various modes and ventilator strategies discussed for supporting pediatric patients with ARDS remains sparse. The lack of data is the primary reason that only weak agreement in expert opinion could be achieved for several of the recommendations included in this section. Future research will be essential to identify the optimal mode, ventilator parameters, and overall management strategy to optimally support and protect the lungs of patients with PARDS at the various points of disease evolution. Furthermore, clinically relevant outcome markers (beyond the classically used outcome measures of mortality and ventilator-free days) must be defined. These could potentially include functional short- and long-term outcome criteria, exercise capacity, and quality of life measures. Despite the multitude of pediatric patients who have been ventilated for acute lung injury, the questions related to optimal ventilator management continue to outnumber the available definitive answers.

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APPENDIX 1. Pediatric Acute Lung Injury Consensus Conference Group

Organizing Committee: Philippe Jouvet, University of Montreal, Canada; Neal J. Thomas, Pennsylvania State University; and Douglas F. Willson, Medical College of Virginia.

Section 1, Definition, incidence, and epidemiology: Simon Erickson, Princess Margaret Hospital for Children, Australia; Robinder Khemani, University of Southern California; Lincoln Smith, University of Washington; and Jerry Zimmerman, University of Washington.

Section 2, Pathophysiology, comorbidities, and severity: Mary Dahmer, University of Michigan; Heidi Flori, Children's Hospital & Research Center Oakland; Michael Quasney, University of Michigan; and Anil Sapru, University of California San Francisco.

Section 3, Ventilatory support: Ira M. Cheifetz, Duke University; and Peter C. Rimensberger, University Hospital of Geneva, Switzerland.

Section 4, Pulmonary-specific ancillary treatment: Martin Kneyber, University Medical Center Groningen, The Netherlands; and Robert F. Tamburro, Pennsylvania State University.

Section 5, Nonpulmonary treatment: Martha A. Q. Curley, University of Pennsylvania; Vinay Nadkarni, University of Pennsylvania; and Stacey Valentine, Harvard University.

Section 6, Monitoring: Guillaume Emeriaud, University of Montreal, Canada; and Christopher Newth, University of Southern California.

Section 7, Noninvasive support and ventilation: Christopher L. Carroll, University of Connecticut; and Sandrine Essouri, Université Pierre et Marie Curie, France.

Section 8, Extracorporeal support: Heidi Dalton, University of Arizona; and Duncan Macrae, Royal Brompton Hospital, United Kingdom.

Section 9, Morbidity and long-term outcomes: Yolanda Lopez, Cruces University Hospital, Spain; Michael Quasney, University of Michigan; Miriam Santschi, Université de Sherbrooke, Canada; and R. Scott Watson, University of Pittsburgh.

Literature Search Methodology: Melania Bembea, Johns Hopkins University.