1 Ventilator Management for Pediatric Acute Respiratory Distress Syndrome

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Clinical Case

A 2-year-old child presents to the emergency department (ED) with poor feeding, fussiness, and tachypnea. His mother reports that he is otherwise healthy, but yesterday he started coughing and developed a fever. The child has been breathing faster than normal over the past 12 hours and has had poor oral intake. In the ED, vital signs include temperature 39.0 C, heart rate 150, respiratory rate 55, blood pressure 90/55, and oxygen saturation 82% on room air. The child is awake but somewhat somnolent. On physical examination, he has nasal flaring, supraclavicular and subcostal retractions, and mild wheezing and rhonchi on auscultation.

- What is the likely diagnosis?
- Does this child meet the definition of pediatric ARDS (PARDS)? If not, what additional data are required to make this diagnosis?
- What is the severity of the child's illness?

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Pathogenesis of Acute Respiratory Distress Syndrome

The clinical presentation of PARDS includes dyspnea, tachypnea, decreased lung compliance, pulmonary edema, and hypoxemia. Acute respiratory distress syndrome (ARDS) is characterized by two major modes of pathogenesis: direct lung injury and indirect lung injury [1]. In pediatric patients, the most common causes of direct lung injury are pneumonia, aspiration, and near drowning, with sepsis as the most common cause of indirect lung injury [2].

The three phases of ARDS are exudative, proliferative, and fibrotic. The exudative phase of lung injury is dominated by direct or indirect lung injury causing an increase in permeability of the alveolar-capillary barrier, with an influx of protein-rich edema fluid, neutrophils, macrophages, erythrocytes, and cytokines into the airspaces causing further damage to the alveolar and bronchial epithelial cells, as well as deactivation of surfactant. This pathophysiologic cascade results in intrapulmonary shunt physiology and arterial hypoxemia.

The flat type I pneumocytes are most sensitive to injury during the acute phase. During the proliferative phase, the cuboidal type II pneumocytes proliferate and differentiate into type I pneumocytes, re-epithelializing the denuded alveolar epithelium to repair the damaged lung segments. Although many patients recover, some

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survivors progress to a chronic fibrosing alveolitis, characterized clinically by chronic hypoxemia, increased alveolar dead space, and decreased pulmonary compliance.

Definition of Pediatric ARDS

In 2015, members of the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed the first reported pediatric-specific definition of ARDS (Fig. 1.1) [3]. Earlier definitions of acute respiratory distress syndrome include the American European Consensus Conference [4] and Berlin [5] definitions and do not include pediatric-specific criteria. The pediatric definition created by PALICC sought to include the unique pathophysiology of PARDS and include consideration of the developmental factors that may influence lung pathology in children. It is important to note the term "acute lung injury" (ALI) was eliminated from the stratification scheme in the 2015 PALICC definition.

The disease severity of PARDS is initially stratified based on noninvasive mechanical ventilation or invasive mechanical ventilation. Considering the increased use of noninvasive mechanical ventilation (i.e., CPAP or BiPAP), the PALICC definition includes patients supported in this manner; however, these patients are not stratified as mild/moderate/severe. In patients supported with invasive mechanical ventilation, disease severity is stratified using oxygenation index (OI) and oxygen saturation index (OSI). Considering pediatric patients are less likely to have arterial catheters as compared to adult patients, diagnostic criteria and disease severity stratification were expanded to include saturation by pulse oximetry. Previous definitions of ARDS relied on PaO_2 by arterial blood gas to make the diagnosis of ARDS. By expanding this definition,

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	**Mild**	**Moderate**	**Severe**
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20[2] PF ratio ≤ 300 SF ratio ≤ 264[1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
	Special Populations			
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing, and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Fig. 1.1 2015 PALICC pediatric acute respiratory distress syndrome (PARDS) definition. [1]Use PaO_2-based metric when available. However, if PaO_2 is not available, wean FiO_2 to maintain $SpO_2 \leq 97\%$ to calculate oxygen saturation index or SpO_2:FiO_2 ratio. [2]For non-intubated patients. [3]Stratification of disease severity by oxygen index or oxygen saturation index should not be used for children with chronic lung disease supported with invasive mechanical ventilation at baseline or children with cyanotic congenital heart disease [3]. (Used with permission)

more patients can be diagnosed with PARDS for treatment and research study purposes.

Other diagnostic criteria similar to previous definitions include chest imaging findings of new infiltrates consistent with acute pulmonary parenchymal disease. The definition was expanded to include unilateral radiographic findings, although this has been debated whether underlying disease pathology in PARDS can cause unilateral lung disease [3]. Timing of onset of PARDS symptoms of hypoxemia and radiographic changes must occur within 7 days of known clinical insult and is used to distinguish from existing chronic lung disease.

Although excluded from previous definitions of ARDS, the 2015 PALICC definition sought to include patients with chronic lung disease (with acute exacerbation), cyanotic congenital heart disease, and left ventricular dysfunction (left atrial hypertension). Diagnosis of PARDS and disease severity is difficult to define in children with chronic lung disease as some of these children are supported with mechanical ventilation and/or supplemental oxygen at baseline. They may also have radiographic findings that meet ARDS criteria at their clinical baseline. Similarly, patients with cyanotic congenital heart disease have low oxygen saturations by definition with a wide spectrum of baseline saturations. Patients with left ventricular dysfunction may develop pulmonary edema with less severe lung injury, considering an elevated baseline left atrial pressure.

It is recommended that all of these at risk populations be considered for diagnosis of PARDS when there is an acute clinical insult, a new finding or change in chest imaging consistent with parenchymal lung disease, and an acute deterioration in oxygenation not explained by changes in cardiac disease. It is important to include these patient groups in the definition of PARDS to allow for earlier diagnosis and therapeutic intervention and to improve the ability to include these patient populations in future research. Limitations to stratification in these patient populations of disease severity based on OI and OSI must be taken into consideration due to the variable, and below normal, baseline.

Clinical Case (Continued)

The child is started on 2 liters per minute (lpm) nasal cannula in the ED with improvement in oxygen saturations to the low 90% range as well as improvement in work of breathing. He is admitted to a pediatric unit but has worsening oxygen saturations over the next 12 h despite increasing oxygen flow. A rapid response is called by the bedside nurse, and the team arrives to find the patient on 4 lpm nasal cannula of 100% oxygen, significant respiratory distress, and oxygen saturation 78%. He is placed on a non-rebreather mask and is transferred to the PICU where he is intubated and started on a conventional ventilator.

- What are the options to improve hypoxemia in this child?
- Are there other less invasive respiratory support options available?
- What ventilator management strategies would you consider in this situation?

Noninvasive Respiratory Support

Although this chapter is focused on current controversies in invasive ventilator management for PARDS, it is important to mention noninvasive respiratory support. Noninvasive respiratory support has had increased use over the last decade, potentially preventing some of the adverse effects caused by invasive mechanical ventilation. These support modalities include high-flow nasal cannula and noninvasive mechanical ventilation devices, including nasal and full-face continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP). As with invasive mechanical ventilation, the benefits of these noninvasive modalities include delivery of high-oxygen concentration to the alveoli and decreased energy expenditure of the respiratory muscles with the added benefit of preserving natural

airway clearance mechanisms. CPAP helps maintain airway and alveolar patency, thereby preventing and/or improving atelectasis, a significant cause of shunt physiology and arterial hypoxemia. Additionally, adding inspiratory pressure with BiPAP helps increase tidal volume delivery in lungs with low compliance, improving alveolar ventilation and reducing $PaCO_2$ [6].

For most patients, noninvasive support devices are well tolerated, reduce the need for sedation, and possibly prevent intubation and mechanical ventilation, generally in patients with more mild disease. Currently, there are only a few studies to support the use of noninvasive respiratory support in children. In one study of 50 children with acute hypoxemic respiratory failure, predominantly secondary to bronchiolitis, supported with BiPAP or standard treatment (face mask oxygen), the patients supported with BiPAP showed a significantly decreased rate of intubation (28%) over those receiving standard therapy (60%, $p = 0.045$) [7]. This study showed noninvasive ventilation improved hypoxemia, tachycardia, and tachypnea as well as prevented some patients from endotracheal intubation and invasive mechanical ventilation. However, another study comparing noninvasive positive-pressure ventilation to inhaled oxygen post-extubation in children 28 days to 3 years of age showed no difference in re-intubation rates (9.1% vs 11.3%, $p > 0.05$) [8]. These studies did not include selection criteria or stratification by ARDS criteria and highlight the need for further studies in the benefits and potential adverse events related to the use of noninvasive respiratory support in the PARDS population.

In light of the current lack of data in patients with PARDS, noninvasive positive-pressure ventilation may be a safe alternative for pediatric patients with mild PARDS and can be considered to prevent intubation in some patients. It could be debated that noninvasive ventilation should only be considered in patients with less severe disease and not used in patients with moderate to severe lung disease. The clinician must understand potential risks associated with these modalities, including the risk of providing inadequate and untimely respiratory support with subsequent cardiopulmonary deterioration in patients with more severe disease. As noninvasive ventilation is trialed, careful and rapid assessment of the patient's response to therapy is necessary. Patients who will respond to therapy will likely show improvement in respiratory distress and oxygenation within the first 30–60 minutes. Clinical vigilance is required to determine if a patient is adequately supported with noninvasive ventilation and whether invasive mechanical ventilation should be pursued.

Lung-Protective Strategies

In the modern era of mechanical ventilation, much attention has been focused on what has been coined "lung-protective strategies" to prevent ventilator-induced lung injury (VILI). The major focus of these strategies is reduction of mechanical stresses on the alveoli, mainly overdistension (volutrauma), cyclic opening and closing of alveoli (atelectrauma), and excessive plateau pressure (barotrauma). Bedside goal-directed strategies, including tidal volume 5–8 ml/kg, positive end-expiratory pressures (PEEP) 10–15 cm H_2O, inspiratory plateau pressure < 28 cm H_2O [9], permissive hypercapnia (pH > 7.25 without a specific target $PaCO_2$), and permissive hypoxemia (SpO_2 > 88%, PaO_2 55–80), are the mainstay of lung-protective ventilator management strategies.

Tidal Volume Delivery: Volutrauma

Prior to the early 2000s, the general approach to mechanical ventilation targeted tidal volumes of 10–15 ml/kg, normal $PaCO_2$, and normal oxygen saturations. It should be noted that the normal resting tidal volume in humans is generally 6–8 ml/kg. In 2000, a landmark study by the ARDS Network showed a significant decrease in mortality in adult ARDS patients with targeted tidal volumes of 6 ml/kg (31%) as compared to "traditional" tidal volumes of 12 ml/kg (39.8%, $p = 0.007$) [10]. The results of this large adult study provided the basis for a significant shift in

the mechanical ventilation management strategies of ARDS patients. In practice, to achieve low tidal volumes and lower inspiratory pressures, a deviation from the goals of normal $PaCO_2$ and PaO_2 (SpO_2) was developed and coined permissive hypercapnia and permissive hypoxemia, respectively.

Although no pediatric study has confirmed a mortality benefit to low tidal volume ventilation in PARDS, pediatric critical care clinicians, in general, have been keen to adopt this strategy for its potential benefit. However, in contrast to the outlined adult findings, it must be noted that observational pediatric studies have shown a relationship between higher tidal volumes and lower mortality [11] or no relationship between tidal volume and mortality [12, 13]. Although they did not find a relationship with mortality, Khemani and colleagues showed higher tidal volumes were associated with increased ventilator-free days. It is important to note these pediatric studies were performed in the era of "lower than traditional" targeted tidal volumes (i.e., <10 ml/kg); thus, a comparison group to the "traditional" ARDS Network tidal volume group of >12 ml/kg is not available. Considering the limitations of observational studies, it is likely these findings represent a heterogeneous severity of disease, with higher tidal volumes seen in patients with better lung compliance (less severe lung injury) with the use of pressure-control ventilation mode. Additionally, in patients with more severe lung injury, physicians likely targeted lower plateau pressures to avoid barotrauma, resulting in lower tidal volumes.

Predicted body weight as compared to actual body weight is recommended when targeting a specific tidal volume as lung capacity is more closely related to height than weight [14]. Targeting predicted body weight may decrease the risk of over distension and volutrauma in obese patients.

The current recommendation for tidal volume management for PARDS, as described by PALICC, is to target tidal volumes of 5–8 ml/kg predicted body weight and as low as 3–6 ml/kg in patients with poor respiratory system compliance [9]. This recommendation is based largely on the findings of the initial adult studies, which have guided the clinical practice of ARDS with lower tidal volume goals. The studies in pediatrics that show lower mortality related to higher tidal volumes have suggested further study is likely warranted to assess a causal relationship between tidal volume and outcome in those with PARDS.

PEEP Titration: Atelectrauma

During normal respiration, the vocal cords close at the end of expiration to maintain a low level of positive pressure in the airways and alveoli to prevent atelectasis. In ARDS, the functional residual capacity of the damaged alveoli decreases, causing atelectasis unless higher mean airway pressure is applied. The use of higher positive end-expiratory pressure (PEEP) may help to avoid repetitive collapse-opening-collapse injury (atelectrauma).

Determining the optimal PEEP at the bedside can to be a difficult task, with methods including incremental increases (decreases) in PEEP while monitoring lung compliance (estimated using tidal volumes, drive pressure, and pressure/volume loops) and radiographic findings. During PEEP adjustment, especially at higher pressures, cardiopulmonary interactions and hemodynamic monitoring must be considered as elevated PEEP (i.e., intrathoracic pressure) may adversely affect central venous return and right ventricular afterload, therefore decreasing cardiac output.

It should be noted that atelectrauma has only been shown in experimental studies [15]. In the era of targeted low tidal volume, three adult trials in ARDS patients evaluating low PEEP vs. higher PEEP showed no significant difference in mortality [16–18]; however, two systematic reviews and meta-analyses suggested a small survival benefit of higher PEEP in patients with severe ARDS [19, 20]. Interesting to the pediatric critical care provider, a pediatric multicenter, retrospective analysis of 1134 patients with PARDS showed that 26% of pediatric patients were managed with lower PEEP than suggested by the ARDSnet protocol based on FiO_2. The investigators found an

increased mortality in that group as compared to the patients in which PEEP was within the protocol (OR 2.05, 95% CI 1.32, 3.17) [21].

PALICC guidelines suggest maintaining elevated levels of PEEP (10–15 cm H_2O) with consideration of higher titration in severe ARDS with attention to limiting the plateau pressure [9]. Considering no pediatric PEEP titration protocol has been studied prospectively, controversy remains as to whether the ARDSnet adult PEEP/FiO_2 titration chart is optimal for both adult and pediatric patients with ARDS.

Plateau Pressure and Drive Pressure (ΔP): Barotrauma

Plateau pressure refers to the equilibrated static pressure at the end of inspiration during an inspiratory hold, which is a result of the tidal volume delivered above PEEP without influence of airways resistance (flow). In pressure control mode of mechanical ventilation, peak inspiratory pressure (PIP) is controlled by the clinician, and ΔP (drive pressure) = PIP − PEEP. The drive pressure is influenced by: (1) airways resistance, (2) chest wall elastance, and (3) alveolar compliance, whereas the plateau pressure reflects the compliance of the alveoli. The tidal volume is then dependent on the compliance of the lung, with worsening lung compliance resulting in lower tidal volumes at the same inspiratory/plateau pressure.

Elevated peak airway pressures may cause trauma simply by pressure injury to the lung parenchyma. Another mechanism suggested for barotrauma is linked to the heterogeneous nature of ARDS, with some alveolar units more affected than others, resulting in different compliance of different lung segments. This may lead to low tidal volumes in poorly compliant lung segments and overdistension in more compliant (and potentially healthier) lung segments. This concept supports the use of pressure control ventilation modes in patients with PARDS, decreasing the risk of over distension of healthier lung segments, although the debate of volume control vs pressure control is more complex than this single point.

Pediatric observational studies have shown both an association between high inspiratory pressures and increased mortality [11, 12] and a lack of association between inspiratory pressure and mortality [13]. None of these studies were randomized or powered to determine the relationship between inspiratory pressure and mortality. A recent adult study in ARDS patients showed the drive pressure to be most predictive of mortality [22]. Whether there is a relationship between peak inspiratory, plateau, and/or drive pressures and mortality in PARDS is yet to be determined.

Based on the available data and clinical expertise, the PALICC recommendation is to maintain plateau pressures <28 cm H_2O, with consideration to increased pressure (28–32 cm H_2O) in patients with increased chest wall elastance (i.e., decreased chest wall compliance), such as those with obesity, chest wall edema, or severely increased abdominal pressure [9]. This recommendation may be considered controversial to some clinicians who argue that a higher plateau pressure (30–32 cm H_2O) in those without decreased chest wall compliance may be safe. Further studies are needed to delineate a "safe" plateau pressure in those with PARDS with the shared goal to decrease secondary lung injury caused by barotrauma.

Clinical Case (Continued)

The patient has been in the PICU for 72 h and continues to have worsening hypoxemia and progressive bilateral infiltrates on chest radiograph. His viral panel is positive for influenza. Despite attempts at lung-protective ventilator strategies including increased PEEP, plateau pressure < 28 cm H_2O, and tidal volume 5–8 ml/kg ideal body weight, his oxygen saturations are consistently ~80–85%. He is on the conventional ventilator in pressure control mode with FiO_2 0.80, PEEP 14 cm

H_2O, and PIP 34 cm H_2O, and now tidal volumes are consistently 3–4 ml/kg. The most recent arterial blood gas is pH 7.31, PCO_2 55 torr, PO_2 50 torr, and SO_2 83%.

- What is the child's P/F ratio, oxygenation index (OI), oxygen saturation index (OSI), and ARDS disease severity?
- What alternative modes of ventilation could you consider at this point?
- What adjunctive therapies would seem reasonable options?

High-Frequency Oscillatory Ventilation

Despite many studies investigating the use of high-frequency oscillatory ventilation (HFOV) for the management of ARDS, this continues to be a topic of significant controversy and debate. Research findings range from showing benefit to causing harm, leaving the clinician without guidance whether to use the modality in their pediatric patients. HFOV works on the principle of lung-protective ventilator management strategy: targeting reduction of atelectrauma, volutrauma, and barotrauma. In this mode, the patient's lungs are inflated using a constant distending pressure, the mean airway pressure (MAP), which helps to decrease cyclic opening and closing of the alveoli, i.e., atelectrauma. High-frequency (5–15 Hz) small tidal volumes may decrease lung injury caused by volutrauma. Disadvantages of HFOV include increased use of sedation and neuromuscular blockade [23], decreased airway clearance and suctioning due to loss of recruitment with circuit disconnections, and decreased ability to transport patients for studies and interventions. Another likely disadvantage due to physician management style, and not the HFOV per se, is slower weaning of mean airway pressure as compared to conventional ventilator due to clinician hesitancy and concern for loss of alveolar recruitment [24].

Although HFOV has been available since the 1970s, there are relatively few studies in pediatrics that help guide the clinician caring for the critically ill child with ARDS. Initial pediatric studies showed improvement in oxygenation parameters [25, 26] but no difference in 30-day mortality [27]. The general consensus at this time was HFOV was safe to use in pediatric patients; however, long-term survival benefit was still to be determined. It is important to note that in these early studies, HFOV was compared to conventional ventilation with high tidal volumes. In subsequent years, adult and pediatric data began to support the use of HFOV, and these data are summarized in a meta-analysis by Sud et al. [28]. Eight randomized controlled trials (two pediatric) from 1994 to 2007 were reviewed in this meta-analysis, with the majority during the era of low tidal volume conventional ventilation strategy. The authors concluded that HFOV might improve survival for hospital or 30-day mortality (risk ratio 0.77, $p = 0.03$, six studies with low bias, 365 patients, 160 deaths). Only one study with five subjects in the final analysis included children.

Two large, randomized controlled studies in adults have helped shape the current management strategies regarding HFOV in adult patients with moderate to severe ARDS. The OSCAR trial [29] showed no significant effect on 30-day mortality between HFOV and conventional ventilation with low tidal volumes and high PEEP. Further, the OSCILLATE trial [23] was stopped prematurely for increased mortality in the HFOV group as compared to the control group (47% vs 35%, relative risk of death with HFOV 1.33, $p = 0.005$). However, results of the OSCILLATE study have come into question, considering the HFOV group had higher mean airway pressures, increased use of vasoactive drugs, sedatives, and neuromuscular blockers.

The most recent data regarding the use of HFOV in children has shown similarly inconclusive results. A secondary propensity score analysis was performed on the subgroup of patients in the RESTORE trial supported with early HFOV as compared to those treated with conventional mechanical ventilation and late HFOV [24].

Of the 2449 subjects enrolled in the trial, 353 patients (14%) were supported with HFOV. After adjusting for risk category, the authors concluded early HFOV was associated with longer duration of mechanical ventilation but no association with mortality. It is important to note this study was not controlled or randomized to these groups, so minimal definitive conclusions can be gained from this analysis.

No conclusive evidence exists that high-frequency oscillatory ventilation is a superior mode of ventilation as compared to "lung-protective" conventional ventilation, with a large randomized controlled adult trial showing it may be more harmful. Despite this HFOV remains a commonly used modality in the respiratory management of PARDS patients and a source of controversy and debate. Inconsistent results supporting negative effects, equipoise, and positive benefit to its use leave the pediatric critical care clinician without guidance as no definitive trial of HFOV has yet been completed in the PARDS population. A randomized, controlled trial of HFOV in patients with severe PARDS is currently being initiated. Hopefully, the role of HFOV for PARDS will be known in the coming years. The PALICC recommendations at this time support "consideration" of HFOV in patients with hypoxemic respiratory failure in patients whose plateau pressure exceeds 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance [9] or 32 cm H_2O in the presence of reduced chest wall compliance.

Adjunctive Therapies

Recruitment Maneuvers

Recruitment maneuvers refer to intermittent increases in airway pressure with the intent of opening collapsed lung units. ARDS patients with predominant lung pathology of diffuse alveolar collapse (as compared to focal consolidation) and inflammatory edema [30] and those without impairment of chest wall mechanics [31] may benefit most from recruitment maneuvers. Pediatric and adult studies have shown recruitment maneuvers to be safe [32, 33] and improve oxygenation [34] in patients with ARDS. No data exist on the effect of recruitment maneuvers on clinically relevant outcomes, such as mortality, morbidity, length of stay, or duration of mechanical ventilation in pediatric patients [35].

In practice, there are several variations to performing recruitment maneuvers. In the authors' opinion, manual recruitment maneuvers are not recommended as the pressure delivered via the bag can be highly variable and difficult to control even with a manometer, risking the negative effects of volutrauma and barotrauma on the lungs as well as decreased cardiac output (decreased venous return, increased right ventricular afterload). Additionally, derecruitment is likely to occur when converting from the manual bag back to the ventilator circuit. Current recommendations support careful recruitment maneuvers to improve severe oxygenation impairment by using slow incremental and decremental PEEP adjustment and recommend not using sustained insufflation maneuvers [9].

Prone Positioning

Prone positioning may improve ventilation-perfusion matching due to shunt physiology related to atelectasis by promoting blood flow to the more open anterior segments (i.e., creating zone 3 conditions) and by mobilizing secretions. The PROSEVA trial, a large adult randomized controlled trial including 466 adults with severe ARDS, showed improvement in 28-day (16.0% vs 32.8%, $p < 0.001$) and 90-day mortality (23.6% vs 41.0%, $p < 0.001$) with prone positioning for at least 16 h/day [36]. Pediatric trials showed improvement of oxygenation while in the prone position [37–39]; however, no change in mortality has been seen [40]. The largest pediatric randomized controlled trial was stopped early due to futility, showing no change in ventilator-free days (primary outcome) or secondary endpoints: time to recovery of lung injury, organ failure-free days, cognitive impairment, overall functional health at hospital discharge or on day 28, or mortality [41]. Systematic reviews showed

improved oxygenation in patients with acute hypoxemic respiratory failure [42] and improved mortality in severe ARDS (PaO_2/FiO_2 ratio < 100) [43], supporting consideration to prone positioning in this specific patient population.

Considering the only large pediatric randomized controlled trial terminated early due to futility, prone positioning is not routinely recommended for PARDS by PALICC [44]. However, this recommendation is debatable when considering the recent adult data showing significant improvement in mortality in adults with severe ARDS. Prone positioning could be considered in severe PARDS patients (with P/F ratio < 100) based on extrapolation from the available adult-based data. A randomized controlled trial of prone positioning in severe PARDS is currently being initiated and will, hopefully, provide greater insight into this management strategy.

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) is a potent pulmonary vasodilator which has been evaluated for use in patients with ARDS. The mechanism of action is relaxation of smooth muscle by increasing intracellular cyclic guanosine monophosphate. In ARDS, delivery of iNO should theoretically preferentially vasodilate and increase perfusion to well-ventilated healthy alveoli, thus possibly decreasing intrapulmonary shunt physiology. Pulmonary vasodilation also results in decreased pulmonary vascular resistance (i.e., right ventricular afterload) when elevated due to hypoxic pulmonary vasoconstriction. Randomized controlled trials in PARDS patients showed transient improvement in oxygenation [45] but no effect on mortality [46]. In 2011 a meta-analysis evaluating the use of iNO in 14 adult and pediatric studies showed transient improvements in oxygenation but no reduction in mortality. The authors noted that iNO may be harmful due to an increased rate of renal failure [47].

Considering the data, iNO is not recommended for routine use in the management of children with ARDS [44, 48]. Inhaled nitric oxide may be considered in patients with pulmonary hypertension and right ventricular dysfunction or, as a temporizing measure, while extracorporeal membrane oxygenation is mobilized in the severely ill patient.

Surfactant

Surfactant is a mixture of protein and lipid produced by type II pneumocytes which helps maintain alveolar patency by decreasing surface tension. Proposed mechanisms for surfactant deficiency in ARDS are direct damage to type II pneumocytes and inactivation of surfactant by protein-rich pulmonary edema fluid during the acute phase of ARDS. With the success of surfactant in the neonatal respiratory distress syndrome population, much excitement has surrounded the potential for restoration of the surfactant system to improve outcomes in the PARDS patient. Early studies and randomized controlled trials showed acute increases in oxygenation [49–52]. One of three larger pediatric randomized controlled trials showed an improved mortality [53], whereas two others showed no effect on mortality [54, 55]. Interestingly, one study showed no improvement in oxygenation with surfactant administration [55]. Current recommendations do not suggest the use of surfactant in the management of PARDS [44].

Clinical Case (Continued)

The patient was transitioned to HFOV on PICU admission day 4 with a mild hypotension that responded to fluid resuscitation. He showed a sustained improvement in both oxygen saturation and the bilateral infiltrates over the following days. After discussions about adjunctive therapies for PARDS, prone positioning was trialed; however, no improvement in oxygenation was seen. Five days later, our patient was transitioned to conventional ventilation and was successfully extubated several days later to 2 lpm via *nasal cannula.*

Important Topics for Further Discussion

Any chapter discussing current controversies in mechanical ventilation for pediatric acute respiratory distress syndrome would not be complete without acknowledging important topics reviewed elsewhere in this book. These topics include extracorporeal support, weaning and extubation readiness assessment, corticosteroid therapy, and sedation management.

Future Directions

Pediatric ARDS continues to be a commonly managed disease with a high mortality [56]. As highlighted in this chapter, significant controversy and uncertainty exist in the critical care management of these patients. Changes in approach to the clinical management of these patients have occurred over the last two decades with a resultant increased trend in survival rate. However, there is still significant controversy and opportunity for research to evaluate benefit and harm of current management modalities and/or combinations of approaches as well as to determine the specific patient populations that may benefit the most from each management strategy. At the same time, it is also important for investigators and clinicians to accept that some treatment modalities may already have sufficient scientific data to support discontinued use in the management of ARDS.

Exciting new lines of research, including biomarkers of lung injury [57], may shed light on goal-directed therapies to identify specific patients that may benefit the most from a particular therapy. Advances in the understanding of the immune system and pharmaceutical modulation will likely benefit the PARDS patient in the future. Also, considering the significant advances in material science and technology over the past few decades, alternative modalities and devices for oxygen delivery [58–60] other than mechanical ventilation should be developed with hope of decreasing the detrimental effects of ventilator-induced lung injury and sequelae of other therapies associated with mechanical ventilation.

Take-Home Points

- Lung-protective mechanical ventilator strategies have significantly reduced mortality in ARDS.
- Current recommendations support consideration of HFOV and recruitment maneuvers but do not currently support the use of inhaled nitric oxide or exogenous surfactant administration. The use of prone positioning remains uncertain.
- There remains significant opportunity for research in the management of PARDS.

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