Pediatric ARDS

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The Pediatric Acute Lung Injury Consensus Conference (PALICC) has provided the critical care community with the first pediatric-focused definition for ARDS. The PALICC recommendations provide guidance on conventional ventilator management, gas exchange goals, use of high-frequency ventilation, adjunct management approaches, and the application of extracorporeal membrane oxygenation for pediatric ARDS (PARDS). Although outcomes for PARDS have improved over the past decade, mortality and morbidity remain significant. Pediatric-specific criteria may provide the ability to more promptly recognize and diagnose PARDS in clinical practice. Improvements in prognostication and stratification of disease severity may help to guide therapeutic interventions. Improved comparisons between patients and studies may help to promote future clinical investigations. Hopefully, the recommendations provided by PALICC, in terms of defining and managing ARDS, will stimulate additional research to better guide therapy and further improve outcomes for critically ill infants and children with ARDS. *Key words: ARDS; pediatric; high-frequency oscillatory ventilation; outcome; children; hypoxemia; hypoxia; ventilator-induced lung injury; prone positioning; nitric oxide; surfactant; extracorporeal membrane oxygenation*. [Respir Care 2017;62(6):718–731.

Introduction

Although representing a relatively small percentage of the total number of pediatric ICU admissions, ARDS is often considered as one of the most challenging patient populations for a clinician to manage. ARDS is an acute lung injury that can be triggered by a heterogeneous set of pulmonary (direct lung injury) and extrapulmonary (indirect ling injury) etiologies. In a comprehensive description of pediatric ARDS,[1] the primary etiologies were pneumonia (35%), aspiration (15%), sepsis (13%), near-drowning (9%), concomitant cardiac disease (7%), and other clinical conditions (21%). Infectious etiologies, including sepsis and pneumonia, represented approximately half of these clinical conditions.

ARDS manifests as pulmonary inflammation, alveolar edema, and hypoxemic respiratory failure. The pathophysiology of this clinical syndrome is characterized by, in progression, inflammatory, proliferative, and fibrotic phases.[2,3] In 1967, a description of ARDS was first provided by Ashbaugh et al.[4] Since then, ARDS has remained a diagnostic and management challenge for clinicians caring for infants, children, adolescents, and adults.

Over the past 5 decades, there have been multiple revisions of the ARDS definition for adult patients, including the Murray acute lung injury score (1998),[5] American-European Consensus Conference definition (1994),[6] Delphi Consensus definition (2005),[7] and Berlin definition (2012).[8] Although these diagnostic criteria were developed primarily for use in the adult population, until recently, they have generally also been employed in the pediatric setting.

It is important to stress that the adult-based definitions of ARDS may not be applicable to pediatrics for a variety of reasons.[9] Anatomic and physiologic differences (Table 1) render infants and children more vulnerable to a severe respiratory insult as compared with adults,[10,11] potentially necessitating a lower threshold for intervention in the pediatric patient. Furthermore, younger patients have a greater metabolic demand and less cardiopulmonary reserve than adolescents and adults. Previous application to pediatrics of the adult-based ARDS definitions, with the requirement to measure arterial oxygenation, may have led to an underestimation of the prevalence of ARDS in pediatrics, given the less common use of arterial lines in infants and children. An additional ongoing concern of the adult-based definitions to the pediatric clinician is the inclusion of P_{aO_2}/F_{IO_2}, which can be influenced by alterations in the applied mean airway pressure (eg, PEEP), as the marker of oxygenation failure. Special considerations are often necessary to optimize management approaches across the heterogeneous pediatric spectrum ranging from neonates to adolescents.

Due to the important limitations of the previous adult-based definitions of ARDS in the pediatric population, the Pediatric Acute Lung Injury Consensus Conference (PALICC) published in 2015 a pediatric-specific definition for ARDS. Unlike the prior adult-based consensus conferences, PALICC offered specific patient management recommendations for pediatric ARDS (PARDS) as well as priorities for potential future research.[12] This review will discuss the PALICC definition and explore the various management options, including conventional ventilation, high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), and weaning/extubation. Last, outcomes after PARDS will be considered.

Defining Pediatric ARDS

In 2015, PALICC, a group of 27 experts from 8 countries, published their recommendations for the definition of pediatric PARDS after a 2-y consensus conference process, which included 3 face-to-face meetings.[12] The PALICC guidelines were developed based on peer-reviewed, pediatric-specific data, as available. For those areas in which pediatric data did not exist, which unfortunately was the situation for many of the areas covered, data were extrapolated from the adult and/or neonatal populations, as applicable. When no data were available, recommendations were generated based on expert opinion. The lack of pediatric-specific data can probably be attributed to the challenges in conducting randomized trials in children with ARDS, including a relatively low incidence of PARDS and the heterogeneity in pathophysiology and physiology across the spectrum of neonates through adolescents. Prior weaknesses in the definition of PARDS as well as inconsistent approaches to mechanical ventilation and adjunct therapies have likely been real hurdles.

A key aspect of the PALICC definition is the lack of age criteria for defining PARDS. However, causes of acute hypoxemia unique to the perinatal period or related to congenital abnormalities are excluded. In contrast to the earlier adult-based definitions, the PALICC definition eliminates the requirement for bilateral pulmonary infiltrates

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Table 1. Differences in Pediatric and Adult Physiology

Feature	Child	Adult
Airway cartilage formation	Incomplete	Complete
Airway resistance	Greater increase in airway resistance with reduction in airway radius	Smaller increase in airway resistance with reduction in airway radius
Chest-wall compliance	Greater compliance in view of incomplete ribcage ossification	Less compliant in view of ribcage ossification
Alveolar maturation and impact on FRC	20–300 million alveoli (age-dependent); lower FRC	300 million mature alveoli; higher FRC
Respiratory muscle reserve	More reliant on diaphragm	Less reliant on diaphragm
Risk of pulmonary vascular remodeling	Greater due to higher pulmonary vascular resistance during perinatal transition	Lower
Metabolic requirements	Higher	Lower

FRC = functional residual capacity

Table 2. Definition of Pediatric ARDS

Age	Exclude patients with perinatal-related lung disease			
Timing	Within 7 d 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 infiltrates consistent with acute pulmonary parenchymal disease			
Oxygenation	Noninvasive ventilation	Invasive mechanical ventilation		
		Mild PARDS	Moderate PARDS	Severe PARDS
	Total face mask bi-level ventilation or CPAP $\geq$ 5 cm H_2O	$4 \leq OI < 8$	$8 \leq OI < 16$	$OI \geq 16$
	P_{aO_2}/F_{IO_2} ratio $\leq$ 300			
	S_{pO_2}/F_{IO_2} ratio $\leq$ 264*	$5 \leq OSI < 7.5$	$7.5 \leq OSI < 12.3$	$OSI \geq 12.3$
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†			
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 that meet oxygenation criteria above†			
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 that meet criteria above not explained by left-ventricular dysfunction			

Data from Reference 13.
* Use P_{aO_2}-based metric when available. If P_{aO_2} not available, wean F_{IO_2} to maintain $S_{pO_2} \leq 97\%$ to calculate oxygen saturation index or oxygen saturation/F_{IO_2}.
† ARDS severity groups stratified by OI or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease.
PARDS = pediatric ARDS
OI = oxygenation index
OSI = oxygen saturation index

on chest imaging due to a lack of evidence that etiology, management, and outcomes differ between patients with unilateral versus bilateral disease (Table 2).[12,13]

In following the Berlin definition,[8] PALICC eliminated the term acute lung injury and recommended that the severity of PARDS be stratified based on the oxygenation deficit as mild, moderate, and severe. To overcome the limitation of using P_{aO_2}/F_{IO_2}, as mentioned above, the PALICC definition relies on the oxygenation index (OI) ($[F_{IO_2} \times \text{mean airway pressure} \times 100]/P_{aO_2}$) or the oxygen saturation index ($[F_{IO_2} \times \text{mean airway pressure} \times 100]/S_{pO_2}$ when an arterial blood gas is not available) to assess the degree of hypoxemia in PARDS.[14,15] It is important to note that the recommendation to apply S_{pO_2} criteria to the PARDS definition requires that oxygen supplementation be titrated to achieve S_{pO_2} in the 88–97% range. Mild PARDS is defined as an OI of 4–8 (oxygen saturation index = 5–7.5), moderate as an OI of 8–16 (oxygen saturation index = 7.5–12.3), and severe as an OI > 16 (oxygen saturation index > 12.3).[8,9] As part of the PALICC proceedings, Khemani et al[13] reported a mortality rate for PARDS of 40% when the OI exceeds 16.

Given the increasingly common use of noninvasive ventilation in pediatrics, PALICC included this ventilatory

approach in the PARDS definition as long as the patient is receiving a minimum CPAP (expiratory positive airway pressure) of 5 cm H_2O. A goal of this aspect of the PARDS definition is to promote earlier diagnosis, and possibly earlier intervention, for those with significant lung injury. Other elements of the PALICC definition, similar to the Berlin definition, include onset within 7 d of a known clinical insult and the presence of respiratory failure not fully explained by cardiac failure or fluid overload.[12,13]

To be as comprehensive as possible, PALICC included recommendations for defining PARDS in infants and children with chronic lung disease, cyanotic congenital heart disease, and left ventricular dysfunction. Given variable baselines, a priori values of OI (or oxygen saturation index) should not be used to risk stratify PARDS in these specialized, higher-risk subpopulations.[12,13]

It is important to emphasize the potential benefits of the PALICC definition. Pediatric-specific criteria may provide the ability to more promptly recognize and diagnose PARDS in clinical practice. Improvements in prognostication and stratification of disease severity may help to guide therapeutic interventions. Improved comparisons between patients and studies may help to promote future research and improve outcomes. Last, a more comprehensive understanding of disease epidemiology may now be possible. The validation of the PALICC PARDS definition will require large multi-center studies across the pediatric spectrum. Such work will, hopefully, help identify and validate thresholds to escalate therapeutic interventions, such as the initiation of ECMO.

Conventional Mechanical Ventilation

Mode of Ventilation

From the start of this discussion, it is important to stress that outcome data do not exist to demonstrate any mode of ventilation to be superior to any other. Thus, PALICC was unable to make a recommendation regarding the ventilatory mode(s) to be used for the management of PARDS. The consensus conference recommended that future studies be designed to assess the potential effects of ventilator mode on clinical outcome.

Tidal Volume

Unlike in the adult population,[16] a randomized control trial of tidal volume (V_T) does not exist for PARDS. Pediatric clinicians are thus left to extrapolate the adult-based recommendation of 6 mL/kg V_T for ARDS to infants and children or rely on observational pediatric data. The studies by Erickson et al[17] and Khemani et al[18] demonstrated an inverse relationship between V_T and mortality in children. The same finding was seen by Zhu et al[19] in infants. For subjects older than 1 y, this study did not show an association between V_T (even when V_T values were < 6 mL/kg or > 10 mL/kg based on ideal body weight) and mortality or ventilator-free days.

These pediatric studies seem to contradict the adult-based 6 mL/kg recommendation[16]; however, these observational studies need careful assessment. It is important to note that the pediatric subjects were generally ventilated with pressure-limited modes of ventilation. Thus, one could speculate that subjects with more severe lung injury were managed with lower V_T levels than those with healthier lungs. Thus, one possible interpretation of the available pediatric data is that subjects with more severe lung disease were managed with lower V_T levels and were more likely to die due to the severity of their underlying lung disease. The reader is cautioned when interpreting observational studies to carefully distinguish the difference between cause and effect and association.

PALICC recommended that for any invasively mechanically ventilated pediatric patient, the delivered V_T should be "in or below the range of physiologic V_T for age/body weight (ie, 5–8 mL/kg predicted body weight) according to lung pathology and respiratory system compliance."[12,20] When evaluating the full component of ARDS data on V_T and outcome (pediatric and adult data), PALICC recommended using "patient-specific tidal volumes according to disease severity. Tidal volumes should be 3–6 mL/kg predicted body weight 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."[12,20]

It is important to stress that the PALICC recommendations stress ideal (predicted) body weight when determining the appropriate V_T to deliver.[20] Because traditional textbooks generally include ideal body weight calculations only for older children, adolescents, and adults, several internet programs have been developed to provide interactive calculators to determine the ideal body weight for pediatric patients as young as 1 y of age. Alternatively, one may estimate the ideal body weight for a child by using the available sex and age growth charts (www.cdc.gov/growthcharts/clinical_charts.htm, *Accessed March 28, 2017*): On the appropriate chart, the patient's height/length can be graphed, and once the height/length percentile is known based on sex and age, the predicted weight that corresponds to this same percentile can be simply determined.[21]

Peak Inspiratory Pressure and Plateau Pressure

Consistent with the ARDS Network study,[16] the publications by Erickson et al[17] and Khemani et al[18] reveal a linear association between mortality and peak inspiratory pressure (PIP). Thus, PALICC recommended that the pla-

teau pressure, in the absence of transpulmonary pressure measurements, should be limited "to 28 cm H_2O, allowing for slightly higher plateau pressures (29–32 cm H_2O) for patients with increased chest wall elastance (ie, reduced chest wall compliance)."[12,20] It should be noted that with the use of variable inspiratory flow ventilation and often uncuffed endotracheal tubes, the pediatric clinician often substitutes PIP for plateau pressure. Such an approach should, theoretically, provide improved lung protection, since the plateau pressure must always be the same or lower than the PIP, depending on the degree of inspiratory airways resistance.

PEEP

PEEP should be titrated to avoid alveolar collapse at end expiration (atelectrauma). Three randomized controlled trials (RCTs)[22-24] in adults with ARDS studied higher versus lower PEEP levels according to PEEP/F_{IO_2} tables but did not analyze PEEP in relation to collapse during end expiration. None of these clinical investigations demonstrated a difference in outcome. However, 2 subsequent meta-analyses suggest that higher levels of PEEP as part of a lung-protective strategy may be associated with lower hospital mortality in adults with ARDS as defined by $P_{aO_2}/F_{IO_2} \leq 200$ mm Hg.[25,26] However, this positive effect of PEEP was not seen in those with more mild forms of acute lung injury. Unfortunately, data are lacking with regard to PEEP management for PARDS.

PALICC recommended that in the absence of definitive pediatric data, moderately elevated levels of PEEP (10–15 cm H_2O) should be titrated in patients with severe PARDS to the observed oxygenation and hemodynamic response.[12,20] PEEP levels $>$ 15 cm H_2O may be needed for severe PARDS with attention paid to limiting the peak airway pressure within the limits described above. PALICC stressed that markers of oxygen delivery, respiratory system compliance, and hemodynamics should be closely monitored as PEEP is increased.

Driving Pressure

Recent data in the adult ARDS population have shown that the driving pressure is more closely related to mortality than PIP or PEEP alone.[27,28] A single SD increment in driving pressure (approximately 7 cm H_2O) was shown to be associated with higher mortality with a relative risk of 1.41.[27] No corresponding data exist for PARDS, and thus PALICC did not address this relatively new concept. Further investigation in the pediatric ARDS population is clearly needed.

Recruitment Maneuvers

The ability to recruit diseased lung depends on several factors, including the type of lung disease (eg, diffuse alveolar disease vs focal alveolar consolidation), time course of the lung disease process, and respiratory system compliance. In general, patients with decreased lung compliance show a poorer response to recruitment maneuvers than those with decreased chest-wall compliance.[29] However, pulmonary pathology characterized predominantly by alveolar collapse (eg, infant respiratory distress syndrome) or inflammatory edema demonstrates a better potential for lung recruitment, despite being characterized mechanically by a low lung compliance state. Application of recruitment maneuvers has been shown to improve oxygenation in adult ARDS (ie, predominantly inflammatory edema) in those without impairment of chest wall mechanics.[30]

With the lack of convincing adult-based data and no definitive pediatric data, significant controversy continues to exist on how best to apply recruitment maneuvers, if at all, in clinical pediatric practice. PALICC recommended that careful recruitment maneuvers by slow incremental and decremental PEEP steps be formed in an attempt to improve severe oxygenation failure. However, sustained inflation was not recommended due to a lack of available data.[12,20]

Gas Exchange Goals

A key underlying principle should always be that oxygenation and ventilation goals be titrated based on the perceived balance between the perceived risk(s) of the toxicity of ventilatory support needed and the potential benefit(s) to the patient. Specific gas exchange goals may vary between patients and often within the same patient over time.

It is important to note that in patients with ARDS, increased systemic oxygenation has not been correlated with improved outcomes.[16,31,32] In the ARDS Network low V_T study, the 6 mL/kg V_T group showed improved survival yet lower average oxygen saturation levels than those managed with 12 mL/kg.[16] The likely explanation is that maximizing oxygenation may require increased ventilator support, thus resulting in increased ventilator-induced lung injury and, subsequently, worse outcomes.

PALICC recommended that for mild PARDS with PEEP $<$ 10 cm H_2O, the S_{pO_2} goal should generally be 92–97%. For those with more severe PARDS with PEEP $>$ 10 cm H_2O, the consensus conference recommended that S_{pO_2} of 88–92% "should be considered" after PEEP has been optimized.[12,20] Such an approach has been termed permissive hypoxemia.[33,34] Although S_{pO_2} values $<$ 88% may be acceptable for some patients, insufficient data exist to make

a general recommendation. Because long-term neurologic and other end-organ (eg, renal) effects of permissive hypoxemia have not been studied, clinicians must consider the potential benefits and risks of this approach for each individual patient. The use of permissive hypoxemia is cautioned against in those with acute intracranial pathology and clinically important pulmonary hypertension as well as in pregnancy.

When oxygen saturations are maintained $< 92\%$, PALICC recommended the monitoring of central venous saturation and markers of oxygen delivery.[12,20] The lower acceptable arterial oxygen saturation target remains controversial for those with severe PARDS. In the absence of data to support a specific lower S_{pO_2} limit, ventilatory approaches should provide adequate tissue/organ oxygenation while minimizing oxygen toxicity and ventilator-induced lung injury.

Similarly, PALICC recommended permissive hypercapnia as a management strategy to minimize ventilator-induced lung injury for patients with moderate-to-severe PARDS.[12,20] Available data suggest that low-V_T, pressure-limited ventilation with permissive hypercapnia may improve ARDS outcome.[35,36] A pH range of 7.15–7.30 was recommended by PALICC within the use of lung-protective guidelines as described previously. Similar to the situation with S_{pO_2}, insufficient data exist to recommend a lower pH limit. Again, the risks and benefits should be assessed for each clinical scenario. Exceptions to the use of permissive hypercapnia include severe pulmonary hypertension, intracranial hypertension, select congenital heart lesions, significant ventricular dysfunction with hemodynamic instability, and pregnancy.

High-Frequency Oscillatory Ventilation

Over the past nearly 3 decades, HFOV has been employed as a rescue modality for patients with refractory hypoxemic respiratory failure. It has been theorized that HFOV provides a lung-protective ventilation strategy by preventing atelectrauma and maintaining airway recruitment via a constant applied airway pressure and preventing volutrauma by avoiding alveolar overdistention via the delivery of V_T less than anatomic dead space.[37]

Since definitive data were lacking to fully assess the efficacy and safety of HFOV for adult ARDS, 2 large multi-center randomized, controlled trials (the OSCILLATE and OSCAR trials) were performed.[38,39] Both studied mortality differences between HFOV and lung-protective conventional ventilation in adults with early moderate-to-severe ARDS.

OSCAR[38] demonstrated no significant difference in all-cause 30-d mortality (41.7% vs 41.1%) and in-hospital mortality (50.1% vs 48.4%) between HFOV and control groups. It is important to acknowledge that ventilator management in the control group varied at each of the participating centers according to local practice. Furthermore, low V_T was encouraged but not required. Also, the majority of the participating units were not experienced with HFOV use, although study initiation did include training.

OSCILLATE[39] studied early use of HFOV with high initial mean airway pressures (30 cm H_2O titrated based on oxygenation to a maximum of 38 cm H_2O) to promote lung recruitment. Increased mortality was seen with HFOV as compared with the lung-protective conventional ventilation group (47% vs 35%, $P = .005$). Of interest, a larger subset of HFOV subjects required inotropic support as compared with the conventional ventilation group (91% vs 84%, $P = .01$). As an associated point, nearly 50% of the subjects studied were septic. Thus, one could speculate that the use of higher mean airway pressures with HFOV might have exacerbated cardiovascular compromise in hemodynamically unstable septic subjects, contributing to the increased mortality seen.

Unfortunately, pertinent pediatric HFOV data are lacking because the only RCT was small and was performed long before the low-V_T era.[40] A retrospective study involving 328 children assessed HFOV use in acute respiratory failure related to multiple etiologies.[41] Mortality risk was associated with OI and underlying diagnosis. Specifically, an elevated OI before starting HFOV and diagnoses of immunodeficiency, cyanotic congenital heart disease, and chronic lung disease significantly predicted mortality risk at 30 d. This study emphasizes that the etiology of respiratory failure may be predictive of the response to HFOV, and the risk of mortality may be more related to underlying disease processes than the use of HFOV per se.

Of importance to the pediatric practitioner, Bateman et al[42] recently published a secondary propensity score analysis of the 353 subjects enrolled in the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study[43] who were managed with HFOV. Early application of HFOV was associated with a significantly longer duration of mechanical ventilation and greater use of sedation and pharmacologic paralysis. However, no mortality association was noted. The authors speculated that the increased length of ventilation with early HFOV use could be related to variations in the management of HFOV (specifically HFOV weaning) across the multiple centers or due to HFOV itself. The lack of randomization of HFOV and the lack of standardization of ventilator management limit the conclusions that can be drawn.

Unfortunately, clinicians continue to lack definitive guidance in the use of HFOV for PARDS. Since the publication of OSCAR and OSCILLATE in 2013,[38,39] adult practitioners have trended away from HFOV use for ARDS. In pediatrics, the use of HFOV for PARDS remains controversial, with practice generally based on institutional ex-

perience. Until additional PARDS studies are performed, HFOV use in pediatrics will probably remain center-dependent and even clinician-dependent.

In returning to the PALICC recommendations, HFOV should be considered as an alternative ventilatory mode for those patients with moderate-to-severe PARDS "in whom plateau airway pressures exceed 28 cm H_2O in the absence of clinical evidence of reduced chest-wall compliance."[12,20] Additional data are clearly needed to assist the pediatric clinician with guidance on HFOV management, including patient selection, optimal oscillator settings, and management (especially weaning) algorithms. Until definitive HFOV outcome data in PARDS can be obtained in a large, multi-center RCT, it seems prudent to adopt the routine use of lung-protective conventional ventilation for PARDS and transition to HFOV in selected patients, followed by aggressive weaning as the disease process(es) resolves and pulmonary compliance improves.

Adjunct Approaches to PARDS

Corticosteroids

Corticosteroid administration is estimated at 20–60% of PARDS patients.[7,44,45] However, the interpretation of this information is clearly confounded by the variety of indications for steroid administration and secondary diagnoses. An RCT[44] of PARDS subjects who received a low dose methylprednisolone infusion showed no differences in mortality or duration of mechanical ventilation, ICU admission, and hospital stay. Corticosteroid therapy was not associated with increased incidence of hyperglycemia or nosocomial infections. It should be noted that interpretation of this study is limited by its small sample size and the exclusion of immunocompromised patients and those with prior steroid exposure.

Published in the same year is a prospective, observational, single-center PARDS study[45] that investigated corticosteroid administration for a variety of indications in a cohort of 283 children. In contrast, this study demonstrated that corticosteroid exposure for >24 h was associated with increased mortality, fewer ventilator-free days (at 28 d), and a longer length of ventilation in survivors as compared with those without corticosteroid exposure or corticosteroid exposure for <24 h. These findings persisted after multivariate and propensity score-adjusted analyses for potential confounders, including severity of illness, OI, multiorgan failure, and immunocompromised status. However, a cause and effect relationship between corticosteroid administration and outcomes cannot be definitively established, given the observational study design.[45]

Given the available pediatric literature, PALICC determined that corticosteroids cannot be recommended as routine therapy for PARDS.[12,46] A large, multi-center, RCT will be needed to further investigate the role of corticosteroid administration for PARDS. Any such study would need to consider corticosteroid use for indications other than ARDS.

Inhaled Nitric Oxide

Inhaled nitric oxide (INO) is, theoretically, an ideal, selective pulmonary vasodilator due to its local activity and very short half-life.[47-49] Because vasodilation predominantly occurs in adequately ventilated regions of the lung, blood is shunted away from more poorly ventilated regions. INO has been postulated as a therapeutic approach to ARDS by reducing ventilation/perfusion mismatch via a reduction in dead space ventilation and a resultant improvement in oxygenation. However, 3 RCTs have been performed in children with ARDS,[50-52] and each has shown that INO does not improve outcome for PARDS, despite the expected short-term oxygenation benefit. This conclusion is supported by the outcome of a meta-analysis of 604 children and adults with ARDS.[53] Potential clinical exceptions in which INO may be indicated for ARDS include patients with documented pulmonary hypertension, as a bridge to ECMO cannulation, and in those with clinically important right-ventricular dysfunction.

Prone Positioning

Adult and pediatric data conflict on the use of prone positioning for ARDS. In the one pediatric RCT investigating the role of prone positioning, Curley et al[32] studied 102 mechanically ventilated pediatric subjects with early acute lung injury ($P_{aO_2}/F_{IO_2} \leq 300$ mm Hg). 90% of proned patients showed improvements in oxygenation as defined a priori as a $\geq$ 20 mm Hg increase in P_{aO_2}/F_{IO_2} or a $\geq$ 10% decrease in OI after a supine-to-prone transition. However, the study was halted at a planned midpoint analysis for futility. Although the process of proning appeared safe,[54] no differences in the primary outcome variable of ventilator-free days or any of the secondary outcome parameters were seen.

In contrast, the adult PROSEVA trial[55] demonstrated improved survival in those with severe ARDS. Several important differences between the pediatric prone study of Curley et al[32] and PROSEVA[55] should be noted. First, Curley et al[32] enrolled a heterogeneous group of subjects ranging from mild to severe lung injury, whereas PROSEVA[55] focused on severe ARDS. Also, the pediatric study mandated the use of HFOV as ARDS progressed and oxygenation worsened. With the current uncertainty of the role of oscillation, this could easily have been a significant confounding variable. Thus, the role of prone position for PARDS remains uncertain, and thus further investigation is warranted.

Exogenous Surfactant

Studies in both the adult and pediatric populations have shown no outcome benefit with the administration of exogenous surfactant for ARDS.[56-58] PALICC concluded that surfactant therapy cannot be recommended as routine therapy for those with PARDS; however, the consensus conference went on to recommend that further study should focus on specific patient populations that may be more likely to benefit as well as specific dosing and delivery approaches.[12,59]

Neuromuscular Blockade

In the adult population, neuromuscular blockade during the initial 48 h of ARDS demonstrated improved survival and time off the ventilator in those with severe lung disease.[60] A recent pediatric study[61] of subjects with acute hypoxemic respiratory failure showed that pharmacologic paralysis resulted in an improvement in OI; however, V_T distribution and regional lung filling characteristics were not affected. Longer term outcomes, including survival, were not assessed. For infants and children, the topic of neuromuscular blockade for PARDS has not been adequately studied to offer any pediatric-specific recommendations.

Summary of Adjunct Therapies

Overall, PALICC concluded that, as a general rule, the routine use of corticosteroids, INO, exogenous surfactant, prone positioning, and neuromuscular blockade cannot be recommended.[46,59] INO should be reserved for those with documented pulmonary hypertension and/or clinically important right-ventricular dysfunction.[59] Prone positioning may be considered in those with severe PARDS, given the available adult data.[59] Future clinical investigations are clearly needed to definitively establish the role, if any, that these adjunct therapies have in the management of PARDS.

Extracorporeal Life Support

The use of venovenous ECMO for refractory ARDS continues to increase, especially in the adult population.[62] Despite decades of use, the optimal timing for cannulation remains uncertain and continues to be controversial. As part of the PALICC proceedings, Khemani et al[13] reported a mortality rate for PARDS of 40% when the OI exceeds 16. Survival rates $>$ 70% have been reported with venovenous ECMO for viral-induced ARDS.[63-65] The key to optimal outcomes for severe PARDS is balancing risk and benefit to cannulate the right patient at the right time. Unfortunately, data to assist with this complex clinical decision-making process are lacking. Furthermore, there is a shortage of definitive management data for the PARDS ECMO patient regarding optimal ventilator management, anticoagulation titration, and other adjunct therapies. Further discussion of the management aspects of the pediatric ECMO patient are beyond the scope of this review.

Given the lack of clear ECMO criteria applicable to individual patients, there was strong consensus by PALICC that decisions to employ ECMO support in children with ARDS be based on "serial structured evaluations of clinical data, including evidence of improving or deteriorating trends."[66] An inability to maintain clinical stability within recommended limits for safe mechanical ventilation management should prompt the clinical care team to consider ECMO cannulation in the absence of contraindication(s).[66]

Weaning and Extubation

Although a detailed discussion of weaning and extubation is beyond the scope of this review, general clinical management thoughts will be offered. In general, gradual weaning from mechanical ventilation toward extubation has been replaced by extubation readiness testing. Having said this, ventilator settings should generally be reduced, especially if above the limits previously discussed, whenever possible to minimize the likelihood of progressive ventilator-induced lung injury. PALICC strongly recommended that an assessment of predefined clinical and physiologic criteria of extubation readiness be performed at least daily to minimize the duration of invasive mechanical ventilation.[12,67] Such testing should assess both muscle strength and endurance.[67]

Although there are no definitive data to support this practice, pediatric patients are not uncommonly extubated to noninvasive respiratory support (eg, noninvasive ventilation or high-flow nasal cannula) in an attempt to maximize the chance for successful liberation from invasive ventilation. Such practices should be the focus of future clinical research investigations.

Outcomes After PARDS

Despite advances in the recognition and management of ARDS, mortality rates remain unacceptable at 29–45 and 22–40% in adults and children, respectively.[13,21,68,69] Of note, the 2013 pediatric surfactant study[58] showed a mortality rate of only 12% in the intervention group and 9% in the control group. However, it must be noted that there were multiple exclusions to study participation, which probably excluded higher-risk patients. Overall, the general trend has been one of decreasing mortality for PARDS, especially for those without preexisting comorbidities.

Current data on long-term outcomes for PARDS survivors remain quite limited. The existing studies are generally small, and their results are probably outdated in the

current era of lung-protective ventilation.[70,71] PALICC recommendations for post-PARDS pulmonary function assessment include screening for pulmonary function abnormalities within the first year after discharge and referral to a pediatric pulmonologist for any patient noted to have a deficit in pulmonary function.[12,72]

One adult-based long-term outcome study of ARDS[73] warrants consideration, given its potential application to pediatrics. Nearly 50% of adult survivors of ARDS had persistent functional disability 12 months after ICU discharge. Most of these subjects were not limited by pulmonary function but rather by extrapulmonary conditions, with weakness and muscle wasting being most prominent. In consideration of these findings, one should consider the potential implications of pharmacologic sedation and immobility generally associated with the management of ARDS.[73,74] The theoretical importance of wakefulness and physical rehabilitation, even while receiving mechanical ventilation and/or ECMO, should be considered.[75-82] Of course, for each individual patient, the risks and benefits must be carefully considered by the clinical care team.

In consideration of the decreasing mortality rates for PARDS, PALICC recommended that research should focus on potential alternative end points. The consensus conference offered the following thoughts for consideration: rate of new or progressive organ dysfunction/failure, treatment/ventilator-free days, duration of supplemental oxygen therapy, risk-adjusted hospital and ICU lengths of stay, metrics of quality of life, neurocognitive functioning, and overall emotional well-being.[12]

Summary

Despite decades of research and experience of managing PARDS patients, there remains a lack of definitive data, especially with regard to clinical management. Although PALICC has provided the pediatric community with a consistent definition for infants, children, and adolescents with ARDS, it remains to investigators to validate the proposed criteria and further correlate the severity classification with outcome. Until definitive pediatric data become available, current recommendations on identification, risk stratification, and management of PARDS will largely continue to rely on expert opinion and extrapolation of data from neonates and adults.

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Discussion

Lin: Ira, I'm interested to hear your thoughts on some of the even more advanced modes of ventilation, specifically APRV (airway pressure release ventilation) or high-frequency percussive ventilation, and their roles in ARDS in the future. Particularly, for APRV to replace the oscillators so you don't have to keep them sedated and paralyzed.

Cheifetz: Excellent question. Most of those advanced modes of ventilation were addressed by PALICC,[1,2] and as I mentioned in my presentation, there are 151 total recommendations. Specifically, in terms of APRV, I need to refer back to the first slide I showed, which simply states that there are no definitive data to support any mode of ventilation over any other. When you review the available APRV

literature, there really are no data to show superiority over any other ventilatory approach. Most of the studies, unfortunately, are quite hard to interpret because of the inherent differences in comparison groups. What do you match when you compare APRV to HFOV or APRV to pressure control ventilation? With HFOV, you cannot match peak pressure; so do you match mean pressure? But what about Δ-P? There really is no way to perform a true head-to-head comparison. Similarly, what would you match between APRV and pressure control ventilation, as the set parameters are inherently different? It's a real challenge. So, if you like APRV and believe it is more optimal for a specific patient's pathophysiology than other approaches, use it. If you don't like it or feel it is not appropriate for an individual patient's pathophysiology, don't use it. In terms of other high-frequency approaches (in addition to HFOV), there are high-frequency jet ventilation and high-frequency percussive ventilation. I did not discuss these in my presentation due to time limitations. For both of these high-frequency modalities, PALICC concluded there are inadequate data to support their use. The wording is important in that PALICC does not say you cannot or should not use them; the statements say their routine use cannot be recommended. It is important to note that in many of the recommendations, the wording is "cannot recommend." Few of the recommendations say "you cannot do X." These types of statements are largely based on the lack of definitive data in the pediatric population with ARDS.

Walsh: Was there any talk about asynchrony and its role in lung injury in ARDS patients?

Cheifetz: There was discussion on this topic at the consensus conference meetings, but it did not result in any recommendations. It was not a key component of the consensus process, and there are not much data that directly address this point in pediatrics. A challenging aspect of patient-ventilator asynchrony in the clinical environment is how to objectively define it.

Walsh: Right. I didn't know whether you talked about it with paralysis: to paralyze or keep someone awake? And if keeping them awake, do you run into the risk of potential asynchrony versus putting them to sleep? There have been some adult data about asynchrony leading to longer length of stay and potentially higher mortality.

Cheifetz: Neuromuscular blockade was discussed in the non-pulmonary treatments section.[3] The PALICC recommendation is to consider neuromuscular blockade if sedation alone is inadequate to achieve effective mechanical ventilation.

Sweet: You may have mentioned this, but did you in PALICC look at other forms of extracorporeal support besides ECMO?

Cheifetz: The extracorporeal life support section focused on venoarterial and venovenous ECMO.[4] We did not specifically discuss extracorporeal carbon dioxide removal or the Novalung. PALICC does state that children with significant alterations in carbon dioxide elimination and those with mild-to-moderate ARDS may benefit from new extracorporeal devices that provide partial respiratory support.

Panitch: Ira, you mentioned management in the absence of measuring transpulmonary pressure; could you comment on the role of esophageal manometry? And should it be used more than it is?

Cheifetz: Personally, I believe esophageal manometry should be used more than it currently is, and it could be very helpful, especially in patients with more severe lung disease. For reasons that are not totally clear, this approach has never gained traction in pediatrics. Years ago, there was a push to use esophageal manometry, and there were folks using it, but the technology and the catheters had real limitations. Some of the catheters were nearly impossible to place in the appropriate position. This monitoring approach fell out of favor and has never came back. In thinking about the oscillator, maybe we could determine a more optimal approach to HFOV if we used esophageal manometry. I do not know whether it will make a comeback or not; I hope so.

Walsh: I wanted to comment on that too, because it says "in the absence of" like everybody uses it. And very few centers actually use it, so it's kind of a weird recommendation. I agree with Ira, the technology is there, but now there's only one manufacturer out there. The catheters you can get from 2 different manufacturers, but the device that actually measures is only one ventilator. You can make your own, which a lot of places are doing, but some places just aren't comfortable with a make-your-own type system, so it makes it hard. We need a device that will measure it for us because we do find transpulmonary monitoring valuable; especially when we get into higher PIPs, we want additional data to help us make the right decisions.

*** Myers:** Ira, a question going back to the Bateman data.[5] Do you think that longer length of stay with high frequency is due to the fact that in a pediatric world, we actually take them back to conventional ventilation before we extubate? And if you're going back at 90% of your mean P_{aw} [airway pressure], those are pretty high conventional settings to go back to, and then wean them down off of conventional ventilation.

Cheifetz: I absolutely agree. I don't know whether we are weaning the oscillator too slowly or, like you said, when we wean, we return to conventional ventilation, which lengthens out the entire weaning process. I believe the problem is that the whole weaning/extubation process from peak lung injury to extubation is too long. If I understand your point currently, I believe your question could be simply stated as: "Can you wean HFOV settings down to CPAP and then extubate?" The answer is "you can," assuming you can get around the sedation requirements, which are often higher with HFOV than conventional ventilation.

Rehder: Same thing about the Bateman data[5]; if I remember correctly, it was duration of ventilation and not ventilator-free days that was longer. Is that correct?

Cheifetz: Correct.

Rehder: So, suggesting that the oscillator potentially keeps patients alive longer but ultimately does not change the outcome.

Cheifetz: Correct, 90-d mortality in the primary propensity score analysis was not different for the early use of HFOV.

Rehder: Right.

Cheifetz: So, survival outcomes are the same, but patients who receive early oscillation are on the vent longer. Here's a real example that I have seen more than once. You have a patient on an oscillator, and the care team's plan is to wean the mean P_{aw} by 1 cm H_2O every 12 h. I see a lot of heads nodding; we have all seen this scenario. Well, of course, it's going to be a long weaning process and, thus, a long duration of ventilation with this type of approach. Who weans any setting on a conventional ventilator by a prescribed 1 per 12 h! One should wean based on physiology and pathophysiology and what the patient needs, not based on a predetermined rate that is not supported by any data. I think we have to move away from that fear of weaning the oscillator too quickly and wean based on the patient's pathophysiology and his/her response to changes in the vent parameters. In summary, I believe the negative HFOV data that have been reported are more linked to the way we have been using the oscillator than to the device per se. Of course, this is only my opinion. I am hopeful that we will study HFOV in PARDS in a randomized controlled fashion in the near future. Until then, the HFOV debate will likely continue.

Walsh: Along the same lines, is it potentially the use of paralytics and sedation when they're on high frequency that may keep them on a little longer? Particularly in our older patients, we end up having to use those, whereas in neonates, they can spontaneously breathe on high frequency and even extubate from high frequency. But we can't do that in our older kids.

Cheifetz: Yes, I fully agree. Sedation and neuromuscular blockade could definitely be confounding variables. This point is supported by the Bateman study.[5]

† **Branson:** So you're telling me that after 30 years of the oscillator, the clinical trials show it's no better, or it's worse! Which is contrary to what Neil [MacIntyre] always tells us, which is that it is not because it doesn't work, "it's because you don't know how to use it right." I still don't understand why it's not dead. Other than that there are people who don't want it to be, not that the evidence keeps it from being dead, just that there are clinicians who don't want it to die.

Cheifetz: That is exactly the controversy. First, I have no conflict of interest, as I have no ties to the device or the company at all. I actually do not believe we have the final answer. You need to look closely at the adult data from OSCILLATE,[6] as I believe it is a study (at least from a pediatric intensivist perspective) that was angled against the oscillator. In most cases, when a clinician oscillates a patient with ARDS, he/she turns up the mean P_{aw}. About half of the OSCILLATE subjects were septic, and many were on multiple vasoactive agents. What happens when you increase the mean airway pressure in a patient who is hemodynamically unstable? They are not going to do well, as right-ventricular preload falls and cardiac output deteriorates. I believe that is what happened in the OSCILLATE trial. One patient scenario in which I would not use the oscillator is septic shock with hemodynamic instability, at least until the capillary leak and need for fluid resuscitation improve. Simply stated, I generally do not oscillate a child in septic shock until they are hemodynamically stabilized. So, I do not think we really know the HFOV answer for PARDS. Again, the RESTORE HFOV data showed that 90-d mortality was no different in the primary propensity score analysis. If you want me to go out on a limb and tell you what I think, I believe in the end we are going to show that HFOV is just another mode of ventilation. Like I mentioned earlier, we have no data that show one ventilatory mode is better than another, and HFOV is likely to be in this same category once we have definitive data for pediatric ARDS. But, I do agree that after all these years, we may not be managing the oscillator in an optimal fashion.

Walsh: Historically, I think synchronized intermittent mandatory ventilation (SIMV) as a primary mode should be retired as well in

our practice, but it's not. It sticks around, and you see people, particularly when you do consensus conferences and those types of things, they stick with what they've always done. Same with using pressure control SIMV as a primary mode, which I also think should go by the wayside, and we should start with volume control because we know tidal volumes are important. And yet we continue to use these antiquated modes of ventilation that historically we have used.

Cheifetz: Brian, what mode do you not want to retire?

Walsh: Seriously though, it's fascinating how we cherry-pick data. I think assist-control volume should be where we start. Why not take a stance and standardize your practice? We gave SIMV a shot at being better; it's not, so let's move on. We know that minute ventilation and tidal volumes are important. Not to mention when you add in SIMV and pressure support, the risk of asynchrony is higher, and so you potentially put your patients at a higher risk for ventilator-induced lung injury. But people won't take a stance and change their practice. There are enough data, but we cherry-pick what we believe.

Cheifetz: I will go back to the first PALICC recommendation in the mechanical ventilation section. There are no data to support any mode of mechanical ventilation over any other. Until we have definitive data, debates like this will continue. Obviously, any of us can argue for whatever mode we like, and someone else across the room will argue for a different mode—both right or both wrong simply depending on perspective, not data!

Rehder: You can certainly make an argument, but there are no data to support either side. There are certainly some things that you can argue are in favor of pressure support ventilation as well.

Smallwood: At the risk of derailing the discussion, I want to get your thoughts on the technological limitations of the oscillator in terms of monitoring sophistication—being able to measure dynamic changes in gas exchange and/or tidal volume. To what degree do you think that has stifled the individualized titration of the mode or the evolution of care over the last 2 or 3 decades? Because it really is a therapy that hasn't changed much. Seriously, the control panel looks like it was stolen from the Apollo space program in the 1960s.

Cheifetz: I completely agree, Craig. As I already mentioned, I do not know that we are using the oscillator optimally, and part of the problem might be that we do not have the right monitoring to do so. I am hopeful that your question is actually an advertisement for your presentation later. And, if not, I will ask this same question when you discuss noninvasive monitoring, electrical impedance tomography, and lung volume assessments. Maybe in the future, these monitoring approaches can help the clinician more optimally manage the oscillator. I eagerly await what you have to say.

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