# 2 Pediatric Acute Respiratory Distress Syndrome: Definition and Epidemiology

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## Introduction

In 1821, Laennec described in his "Treatise on Diseases of the Chest" probably the first published description of ARDS. Laennec described the gross pathology of the heart and lungs as idiopathic anasarca of the lungs – pulmonary edema without heart failure. By the 1950s, pulmonary edema had become a medical entity; however, no distinction was made at that time between cardiac and noncardiac causes. For a period of time, ARDS went by the name of inciting injuries (shock lung, posttraumatic lung, Da Nang lung, etc.). It was not until 1967, in a landmark article published in Lancet, that the term acute respiratory distress syndrome (ARDS) was mentioned [1]. Ashbaugh and colleagues described a syndrome of tachypnea, hypoxia, and decreased pulmonary compliance in a series of 11 adults and one child with respiratory failure. The pathologic features included interstitial and intra-alveolar edema and hemorrhage, as well as hyaline membrane formation.

Like other clinical syndromes, ARDS lacks a definitive gold standard for diagnosis. Histopathology is impractical for real-time clinical applications, no definitive biomarker is present in all cases, and there is a spectrum of the degree of injury. While elements of the pathobiology continue to be established, in vitro and in vivo models have improved the fundamental understanding of the pathobiology of ARDS. As such, our diagnostic criteria have sought to identify clinical signs and symptoms reflective of this pathobiology related to the diffuse albeit nonhomogeneous nature of the injury at both the alveolar epithelial and endothelial surface, inflammation, loss of functional residual capacity and impairment in pulmonary compliance, hypoxemia, and elevations in alveolar dead space.

In 1994, the American European Consensus Conference (AECC) defined ARDS as a syndrome of inflammation and increased permeability in the lungs that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension [2]. For years, pediatric practitioners used the AECC definition of ARDS for clinical care, research, and prognostication.

While this definition was used for nearly 30 years, there were several limitations of the AECC definition of ARDS related to the influence of ventilator settings on hypoxemia, the timing of disease, use of noninvasive ventilation, defining a spectrum of hypoxemia severity in ARDS, and how to specifi-

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cally handle left ventricular dysfunction. These limitations were addressed by the Berlin definition in 2012. While some of these issues are common between adults and children with ARDS, pediatric-specific considerations were not included in either Berlin or AECC definitions [3, 4]. Although there are similarities in the pathophysiology of ARDS in adults and children, pediatric-specific practice patterns, comorbidities, and differences in outcome necessitated a pediatric-specific definition [5].

In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) published specific definitions for pediatric ARDS (PARDS) (Table 2.1) and those gauged to be at risk for PARDS (Table 2.2), as well as recommendations regarding management and suggested priorities for future research [6]. PALICC was a two-year process that consisted of 27 experts from eight countries on three continents. The group was tasked with determining whether the Berlin crite-

**Table 2.1** PARDS definition

<table>
<tr><td rowspan="5">Age: Exclude patients with perinatal-related lung disease<br>Timing: Within 7 days of known clinical insult<br>Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload<br>Chest imaging: Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease</td><td colspan="3">Oxygenation</td></tr>
<tr><td colspan="3">Noninvasive mechanical ventilation: Full-face mask bi-level ventilation or CPAP ≥ 5 cm $H_2O$[b] with PF ratio ≤300 or SF ratio ≤ 264[a]</td></tr>
<tr><td colspan="3">Invasive mechanical ventilation</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>4 ≤ OI < 8<br>5 ≤ OSI < 7.5[a]</td><td>8 ≤ OI < 16<br>7.5 ≤ OSI < 12.3[a]</td><td>OI ≥ 16<br>OSI ≥ 12.3[a]</td></tr>
<tr><td colspan="4">Cyanotic heart disease: Standard criteria with an acute deterioration in oxygenation not explained by underlying cardiac disease<br>Chronic lung disease: Standard criteria with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline<br>Left ventricular dysfunction: Standard criteria with chest imaging changes and acute deterioration in oxygenation not fully explained by left ventricular dysfunction</td></tr>
</table>

OI = oxygenation index = ($FiO_2$ × mean airway pressure × 100)/$PaO_2$
OSI = oxygen saturation index = ($FiO_2$ × mean airway pressure × 100)/$SpO_2$
[a]Use $PaO_2$-based metric when available. If $PaO_2$ not available, wean FiO2 to maintain SpO2 ≤ 97% to calculate OSI or SF ratio
[b]For non-intubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation, see Table 2.2 for at-risk criteria

**Table 2.2** At risk of PARDS definition

<table>
<tr><td rowspan="4">Age: Exclude patients with perinatal-related lung disease<br>Timing: Within 7 days of known clinical insult<br>Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload<br>Chest imaging: Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease</td><td>Oxygenation</td></tr>
<tr><td>Nasal mask CPAP or BiPAP<br>$FiO_2$ ≥ 40% to attain $SpO_2$ 88–97%</td></tr>
<tr><td>Oxygen via mask, nasal cannula, or high flow<br>$SpO_2$ 88–97% with oxygen supplementation at minimum flow[b]:<br><1 year: 2 L/min<br>1–5 years: 4 L/min<br>5–10 years: 6 L/min<br>>10 years: 8 L/min</td></tr>
<tr><td>Invasive mechanical ventilation<br>Oxygen supplementation to maintain $SpO_2$ ≥ 88% but OI < 4 or OSI < 5[a]</td></tr>
</table>

[a]If $PaO_2$ not available, wean $FiO_2$ to maintain $SpO_2$ ≤ 97% to calculate OSI
[b]Given lack of available data, for patients on an oxygen blender, flow for at-risk calculation = FiO2 × flow rate (L/min) (e.g., 6 L/min flow at 0.35 FiO2 = 2.1 L/min)

ria for ARDS, created by adult practitioners and validated with data from adult patients with ARDS, was applicable in children. The Berlin definition of ARDS was seen as an iterative improvement, and although there is value in having a single definition applicable to all ages of patients, pediatric-specific shortcomings of the Berlin definition were identified in relation to (1) whether age or stage of lung development affects the definition of ARDS, (2) the importance and reliability of radiographic criteria, (3) respiratory criteria for severity of disease and risk stratification, (4) the increasing use of noninvasive respiratory support and noninvasive monitoring for acute hypoxemic respiratory failure, and (5) the ability to diagnose ARDS in patients with pediatric pulmonary and cardiac comorbidities. Aspects of the Berlin definition related to (6) timing of disease and (7) coexistence of cardiac disease and ARDS with methods to define left ventricular dysfunction were likely to be similar across a spectrum of age, with some pediatric-specific modification.

## Definition of Pediatric ARDS (PARDS) by the Pediatric Acute Lung Injury Consensus Conference

The Berlin and PALICC definitions of ARDS are similar in regard to the development of signs and symptoms within 7 days of a clinical insult and the development of pulmonary edema that is not fully explained by cardiac failure of fluid overload. Unlike the Berlin definition, the PALICC definition does not require bilateral infiltrates on chest radiograph, incorporates pulse oximetry metrics when $PaO_2$ is not available, introduces the use of oxygenation index (OI) and oxygenation saturation index (OSI) to stratify severity groups instead of $PaO_2/FiO_2$ (PF ratio) with minimum positive end-expiratory pressure (PEEP), and creates specific criteria to define PARDS in children with chronic lung disease and cyanotic heart disease. In addition, no upper limit of age is defined for PALICC criteria, although children with perinatal-related lung injuries are excluded. Moreover, PALICC had pediatric-specific criteria to define PARDS and at risk for PARDS in infants and children on noninvasive ventilation.

## Rationale for Age Criteria

PALICC specifically excludes children with perinatal-related lung disease from the PARDS definition, although there is no upper limit for age. Although the pathobiology of acute lung injury caused by perinatal events such as aspiration of meconium or group B Streptococcus may be similar to the diffuse inflammatory and injury mechanisms of PARDS, the unique pathophysiology related to persistent fetal circulation, changes in perinatal pulmonary vascular resistance, and the processes of care by neonatologists as compared with pediatric intensivists made it important to consider this group of patients separately. In response to this, a similar consensus conference was convened to create a neonatal definition of ARDS, which has many similarities to the PALICC definition [7].

The PALICC definition has no upper limit of age, because there was no clear break point in the incidence or mortality of ARDS, sepsis, or pneumonia between adolescents and young adults [8–12]. Furthermore, there is no clear break point at which critically ill patients are no longer cared for by pediatric intensivists. Increasingly, there are patients in their twenties cared for by pediatric practitioners, and many adolescents are cared for in adult institutions. As such, there is no clear age cut point at which a patient with ARDS should be considered “pediatric” versus “adult.” In order to reduce confusion and improve recognition of ARDS, PALICC recommended health care providers caring for adolescents and young adults should use the definition of ARDS with which he or she is most familiar.

## Timing and Triggers

Acute onset has been included in definitions of ARDS to differentiate ARDS from existing chronic lung disease. In the AECC definition, acute onset was mandated but timing was not

specified; in the Berlin definition ARDS onset was mandated to be within 1 week of a known clinical insult or new or worsening respiratory symptoms [2, 4]. Review of both the pediatric and adult literature identified key similarities in the timing of ARDS after an inciting event such as sepsis, trauma, or aspiration, with most of patients developing symptoms within the first 24 hours and almost all within 7 days [13–19].

Some subgroups of patients develop ARDS very quickly. For example, transfusion-related acute lung injury (TRALI) is defined as ARDS that develops within 6 hours of a transfusion [20, 21]. Similarly, neurogenic pulmonary edema develops rapidly following intracranial insult, typically from traumatic brain injury or subarachnoid hemorrhage [22]. Likewise, ARDS usually develops promptly in the setting of pediatric drowning-related lung injury [23].

## Coexistence of ARDS with Left Ventricular Failure/Dysfunction

The issue of left ventricular (LV) dysfunction/failure is specifically addressed by both the AECC criteria and the Berlin criteria. The goal is to differentiate hydrostatic causes of pulmonary edema from ARDS. In the original AECC criteria, the presence of left atrial hypertension (pulmonary capillary wedge pressure > 18 mm Hg or clinical evidence of left atrial hypertension) was an exclusion criterion for ARDS. Berlin revised this to allow ARDS to coexist with left ventricular dysfunction, as long as there are clear risk factors for ARDS. If not, objective assessment to exclude cardiac failure (echocardiography) should be performed. PALICC concluded that these phenomena are similar in children. Varying degrees of left ventricular dysfunction are frequently reported in children with ARDS and may be associated with increased mortality [24, 25]. Furthermore, echocardiography is widely used in pediatrics to quantify ventricular function and is a good predictor of cardiac symptoms and outcomes in children with left ventricular failure [26].

## Radiographic Findings in PARDS

Both AECC and Berlin definitions of ARDS require the presence of bilateral pulmonary infiltrates on chest radiograph. The primary argument to include bilateral infiltrates in the definition of ARDS is to allow for discrimination between localized processes such as lobar pneumonia and the diffuse inflammatory processes seen in both lungs with ARDS. However, PALICC removed the requirement for bilateral infiltrates, instead requiring patients had evidence of pulmonary parenchymal disease. The main arguments for the removal of bilateral infiltrates surrounded (1) the lack of sensitivity of chest radiographs to detect all pulmonary parenchymal inflammation and edema, (2) that opacification on chest imaging often lags behind hypoxemia, and (3) that the presence of bilateral infiltrates on chest radiograph does not seem to impart additional risk for poor outcome not otherwise captured with the degree of hypoxemia. PALICC elected not to eliminate radiology altogether from the definition to help differentiate other causes of acute hypoxemic respiratory failure, which do not share the pathophysiology of ARDS (i.e., asthma without coexisting pneumonia). However, because there is some evidence to suggest that the presence of bilateral infiltrates may have prognostic relevance in certain subgroups of patients, radiographic data should be included in the design of research studies for enrollment stratification or subgroup analyses based on the presence or absence of bilateral infiltrates.

## Respiratory Criteria for Disease Severity

Unlike the Berlin definition, PALICC allows for the use of pulse oximetry criteria when an arterial $PaO_2$ is not available and recommends the use of oxygenation index (or oxygen saturation index) instead of PF ratio for those on invasive mechanical ventilation.

PALICC argued that pulse oximetry criteria are crucial to define ARDS in children because arterial

lines are not used in all ventilated children. Increasingly, arterial blood gases or arterial line monitoring are reserved for patients with hemodynamic instability or severe hypoxemia. Requiring arterial blood sampling would lead to a significant underrecognition of children with PARDS and make the definition subject to selection bias based on provider preference in obtaining an ABG. Investigators have highlighted that even after stratifying for similar degrees of hypoxemia, mechanically ventilated children with ABGs are sicker, have higher severity of illness, and are on more vasopressor support [27]. Furthermore, several studies have validated that $SpO_2$-based criteria have a strong clear predictable relationship with $PaO_2$-based criteria, validating both $SpO_2/FiO_2$ ratio and the oxygen saturation index. However, it is important to remember that theses metrics require that the $SpO_2$ be ≤97% since the oxyhemoglobin dissociation curve is nearly flat when $SpO_2$ is >97% [25, 28–32].

## OI Versus PF Ratio

The Berlin definition for ARDS accounts for differences in ventilator management by requiring a minimal PEEP of 5 cm $H_2O$ or CPAP of 5 cm $H_2O$ for noninvasively ventilated adults. A minimum PEEP of 10 cm $H_2O$ was considered to define severe ARDS, but this requirement was removed from the definition because it did not discriminate increased risk of mortality as compared with a PEEP of 5 cm $H_2O$. It is important to note that most patients included in the validation of the Berlin criteria were enrolled in ARDSNet studies, and oftentimes PEEP management was protocolized with a PEEP/$FiO_2$ table, with over 50% of patients having a baseline PEEP >10 cm $H_2O$ [3, 4, 33, 34]. Pediatric intensivists generally use less PEEP than their adult colleagues [25, 28, 35], are more variable in how PEEP is applied as a function of hypoxemia, and less frequently escalate PEEP above 10 cm $H_2O$ [35, 36]. This may be important because observational data suggests that failure to escalate PEEP as hypoxemia worsens is independently associated with mortality in PARDS [37].

While some investigators recommend assessing PF ratio on standard ventilator settings (i.e., PEEP of 10 cm $H_2O$) [38], PALICC determined that requiring specific ventilator manipulations may impair recognition of PARDS by clinicians. Instead, PALICC elected to use oxygenation index (OI = [$FiO_2$ × mean airway pressure × 100] ÷ $PaO_2$) to account for the degree of ventilator support. Cut points were derived and validated using existing datasets and the risk of death nearly doubled for each successive cut point: OI < 4 (at risk for PARDS), 4–8 (mild PARDS), 8–16 (moderate PARDS), and > 16 (severe PARDS) with a relatively equal distribution of patients within the mild, moderate, and severe groups. Like the Berlin definition, PALICC developed PARDS severity groups to facilitate common definitions for future research and therapies targeting children with different degrees of lung injury. Given clear differences in mortality and outcome based upon disease severity, as well as potential differences in pathophysiology, risk-benefit profiles may differ based upon disease severity [39, 40].

## Pulse Oximetry Versus $PaO_2$

Fewer arterial blood gases are obtained in pediatric ICUs, and the use of noninvasive respiratory support has resulted in increasing number of patients with lung injury that are cared for outside of ICUs [35, 41–43]. Therefore, it was imperative to create a definition for PARDS that did not rely upon the subjective decision to obtain an ABG [44]. Given the strong linear relationship between oxygen saturation index [OSI = ($FiO_2$ × mean airway pressure × 100)/$SpO_2$] and OI when the $SpO_2$ is ≤97%, PALICC established OSI cut points to correspond with the OI cut points proposed earlier [31]. The SF ratio also has a strong relationship with PF ratio [31, 32, 45], particularly for those on invasive mechanical ventilation. It is unclear how well SF ratio performs in relation to PF ratio for children receiving noninvasive ventilation, given difficulties in calculating delivered $FiO_2$ and the potential effect of modification based upon the degree

of ventilator support. For this reason, PALICC did not recommend applying SF ratios for non-intubated patients (or those not on full-face mask noninvasive ventilation) to grade severity, but rather created guidelines based on combinations of $SpO_2$ and minimal delivered oxygen to establish who is at risk for PARDS. Unfortunately, conventional methods of estimating the fraction of delivered oxygen ($FdO_2$) for those on nasal modes on NIV may over- or underestimate $FiO_2$ depending on the rate of flow delivered to the patient, the patient's minute ventilation, and whether the flow is warmed or humidified. The published guidelines for the calculation of $FiO_2$ by the American Association of Respiratory Care (AARC) suggest that nasal cannula do not provide a $FiO_2$ greater than 40% [46–49].

PALICC recommended that patients who are on full-face mask modes of noninvasive ventilation with a minimum CPAP of 5 cm $H_2O$ who have PF ratios ≤300 or SF ratios ≤264 be considered to have PARDS. Patients who are on full-face mask CPAP or BiPAP but do not fulfill all the criteria for PARDS should be considered at risk for PARDS. To apply $SpO_2$ criteria to diagnose PARDS, oxygen therapy must be titrated to achieve an $SpO_2$ between 88 and 97%.

## Defining PARDS in Children with Existing Lung or Cardiac Disease

A number of exclusion criteria related to gestational age, preexisting chronic lung disease, cyanotic congenital heart disease, and coexisting left ventricular failure/dysfunction have been applied in variable ways in previous PARDS investigations. PALICC sought to standardize criteria in these subpopulations to facilitate future research and clinical care because these preexisting comorbidities do not exclude the potential for these patients to develop PARDS, and these comorbidities represent important at-risk patient populations.

The most important factor in the diagnosis of PARDS in patients with preexisting lung disease is the acute deterioration in oxygenation in response to a known clinical trigger. This is important because at baseline these children may have evidence of pulmonary parenchymal disease on chest imaging and may be on invasive or noninvasive mechanical ventilation. Hence, PALICC recommends that patients with preexisting chronic lung disease who are treated with supplemental oxygen, noninvasive ventilation, or invasive ventilation via tracheostomy should be considered to have PARDS if they have acute changes that meet standard PARDS criteria (acute onset, a known clinical insult, chest imaging supporting new-onset pulmonary parenchymal disease) and have an acute deterioration in oxygenation from baseline which meets oxygenation criteria for PARDS.

Patients with cyanotic congenital heart disease have not been addressed in either the AECC or the Berlin criteria. In general, the presence of cyanotic congenital heart disease has been considered an exclusion criterion for the diagnosis of ARDS in children. This is understandable as intracardiac mixing or right-to-left shunting of blood affects the PF ratio and other indices of oxygenation. However, it is clear that PARDS can occur in children with cyanotic congenital heart disease [50]. Hence, worsening hypoxemia with pulmonary parenchymal disease on chest radiograph in the absence of changes in the underlying cardiac disease may be consistent with a diagnosis of PARDS.

The diagnosis of ARDS in these children requires individual providers to exclude new changes in intracardiac shunt/mixing or worsening left ventricular dysfunction as the cause of worsening hypoxemia. Unfortunately, there are limited objective criteria to exclude new changes in intracardiac shunt. Echocardiography has limitations, although it may be useful in excluding selected cardiac causes of acute deterioration in oxygenation (e.g., systemic-pulmonary shunt thrombosis or narrowing, increasing right ventricular outflow tract obstruction, increasing pulmonary hypertension). More invasive modalities such as cardiac catheterization, CT angiography, and magnetic resonance imaging (MRI), while useful in defining intracardiac shunts, pose significant risks in children with ARDS. Hence,

PALICC chose a pragmatic approach, stating patients with cyanotic congenital heart disease are considered to have PARDS if they fulfill standard criteria (acute onset, a known clinical insult, chest imaging supporting new-onset pulmonary parenchymal disease) and have an acute deterioration in oxygenation not explained by the underlying cardiac disease.

## Incidence and Epidemiology

Using the AECC definition, the incidence of ARDS in US, European, Australian, and New Zealand children is estimated at 2.0–12.8 per 100,000 person·years [19, 24, 38, 44, 51]. A series of observational studies in the 1990s and 2000s found that ARDS occurs in 3–6% of PICU patients and between 5 and 8% of mechanically ventilated PICU patients. ARDS mortality in children appears to be lower than in adults (18–27% vs 27–45%) [8, 14, 52–54], although, there are some populations in which adult and pediatric ARDS mortality appears similar (35%) [9, 15, 25, 38, 55]. A recent systematic review and meta-analysis [65] has found that the overall pooled mortality (including the control arm of RCTs and observational studies) for PARDS was 24% (95% CI 19–31) and has been improving over time.

Most pediatric studies report an increased incidence of ARDS in males versus females, but males do not seem to have increased mortality from ARDS [9, 14, 24, 25, 35, 52–54, 57, 58]. Preexisting comorbidities are common among PARDS patients (12–74%) and may be associated with higher mortality [9, 16, 24, 35, 38, 53, 54, 56]. Immunodeficiency is a common preexisting condition, and most studies show increased mortality among immunodeficient patients who develop PARDS [9, 14, 24, 53, 54, 57, 58]. PARDS triggers may contribute to differences in outcome between children and adults or even among children, but pneumonia, sepsis, aspiration, and trauma account for 63–92% of ARDS in both adults and children [8, 9, 14, 24, 25, 35, 38, 54]. Likewise, there may be differences in the rates of pulmonary and extrapulmonary sepsis between children and adults, but the lack of uniformity in the reporting of pulmonary and extrapulmonary etiologies and mortality in ARDS patients makes direct comparison difficult [59, 60]. The PALICC definition is likely to identify many more patients with PARDS, which will likely change both the incidence and mortality rates.

## Validation of the PALICC Guidelines in Recent Publications

Parvathaneni et al. [61] compared the PALICC, AECC, and Berlin definitions among children admitted to a single multidisciplinary PICU in the United States. They found that the PALICC criteria nearly doubled the number of patients diagnosed with PARDS, largely because of the pulse oximetry–based criteria in PALICC. Nearly all patients who met Berlin or AECC criteria also met PALICC criteria. The overall mortality for those who met Berlin or AECC criteria was approximately 30% compared to 22% for those who met PALICC criteria. Approximately 40% of the patients who only met PALICC criteria had mild PARDS and 11% were on NIV, but 20% had severe PARDS, with 31% mortality. Furthermore, for patients in whom both PALICC and Berlin criteria were met, PALICC identified ARDS approximately 12 hours earlier. Interestingly, it appeared as if those with severe PARDS had substantially higher mortality than those with mild to moderate PARDS, with minimal mortality difference between those with mild or moderate PARDS.

Yehya et al. [62] conducted a prospective study looking at variables associated with mortality and ventilator-free days at 28 days among PARDS patients at a single tertiary/quaternary ICU in the United States. This cohort was restricted to children who met criteria with an arterial blood gas (PF ratio for AECC and Berlin, OI for PALICC) and similarly identified that nearly all patients who met AECC or Berlin criteria also met PALICC criteria. They found that neither Berlin $PaO_2/FiO_2$ nor PALICC OI categories at onset of PARDS could discriminate mortality. However, 24 hours after PARDS onset,

there was a stepwise increase in mortality as severity increased (with both PALICC and Berlin groupings).

Rowan et al. [63] investigated whether PALICC criteria discriminated mortality in hematopoietic stem cell transplant (HSCT) recipients requiring invasive mechanical ventilation in multiple PICUs in the United States. Using intubated HSCT patients without PARDS as the reference population, there was no difference in the OR of mortality between HSCT patients with no PARDS versus mild PARDS (OR 1.1, 95% CI, 0.3–4.2; $p = 0.84$) and no PARDS versus moderate PARDS (OR = 1.8, 95% CI, 0.6–5.5; $p = 0.31$) group. The severe PARDS group had a significantly higher risk of mortality with an OR of 6.1 (95% CI, 2.1–17.8; $p < 0.001$). The nonsurvivors were more likely to have multiple consecutive days at moderate to severe PARDS ($p < 0.001$). Most (70%) of the patients met PARDS criteria by day 1 of mechanical ventilation and 89% met criteria by day 3. The moderate and severe PARDS patients had longer PICU length of stay and longer course of mechanical ventilation.

Wong et al. [64] evaluated the PALICC criteria in a multicenter study in Asia. They found that the PALICC criteria for stratification into mild, moderate, and severe groups were associated with a stepwise decrease in ventilator-free days and a stepwise increase in short-term and intermediate-term mortality. The overall mortality in this study was 30.3%, which is comparable with overall PARDS mortality reported in other studies in Asia, although different than what is reported in the United States and Europe.

The Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) study [66] prospectively evaluated PALICC criteria in approximately 170 international intensive care units, representing 27 countries. PARDIE found that using the PALICC definition, PARDS occurs in approximately 3% of children admitted to the PICU, or 6% of those on mechanical ventilation. The incidence of "at risk for PARDS" is undoubtedly higher, and a substantial number of these children (32% in one single-center study of children with bronchiolitis) will subsequently be diagnosed with PARDS. In PARDIE, mortality was similar (approximately 15%) for those who have noninvasive ventilation, mild, or moderate PARDS, with significant higher mortality (>30%) for those with severe PARDS. A delayed measure of PARDS severity (6 hours after PARDS onset) appears to better stratify mortality risk than initial PARDS severity. The PALICC definition identified approximately 40% more children as having PARDS and diagnosed PARDS a median 12.8 hours sooner than the Berlin definition within the first 3 days. PALICC definitions by use of oxygenation index or oxygenation saturation index measurements seem to stratify mortality better than the Berlin PF-based severity groups. Bilateral opacifications were identified in 75% of PARDS patients at the time of PALICC PARDS diagnosis, and 87% of patients had bilateral infiltrates within 3 days of PARDS diagnosis.

## Where Do We Go from Here?

The PALICC definition was meant to be a starting point to unite the PARDS community in establishing a pediatric-specific definition to be used for clinical care and research. Further external validation of this definition is crucial, which should continue to be a focus of investigation. Based on the validation studies conducted to date, it is clear that the PALICC definition is capturing patients who have met previous definitions of ARDS (oftentimes earlier than previous definitions), plus another subset of patients. A substantial proportion of these patients simply do not meet historical criteria because of changes in clinical practice with regard to the use of arterial catheters. Interestingly, the reported incidence of PARDS with the PALICC definition is comparable to historical studies using AECC definition, prior to practice changes related to pulse oximetry and arterial blood gases. Hence, it is possible that the PALICC definition has now just better aligned to our evolution in clinical practice and has not fundamentally changed the epidemiology of the disease.

The elimination of bilateral infiltrates in the PALICC definition is among the most controversial changes and is a departure from both adult and neonatal ARDS definitions. Diffuse inflam-

mation is a crucial element in the pathobiology of ARDS, and bilateral lung opacifications have historically been used as a clinical sign to characterize this inflammation. Given limitations in the ability for routine chest radiographs to consistently characterize this inflammation, the PALICC definition chose to eliminate the requirement with the argument that this inflammation be adequately captured by other elements of the definition (such as hypoxemia). The PARDIE study has highlighted that nearly all patients who meet PALICC criteria are gauged to have bilateral infiltrates within 3 days of PARDS diagnosis and that the absence of bilateral infiltrates is not associated with outcome when controlling for other factors. It also confirmed high levels of disagreement on the interpretation of bilateral infiltrates. The importance of chest imaging in the diagnosis of PARDS should continue to be a focus of PARDS research and should continually be reevaluated if more specific methods for chest imaging are incorporated into routine clinical practice. When constructing a definition, it is crucial that the diagnostic criteria can be applied in all environments likely to treat the disease and is not practitioner dependent.

Like the Berlin definition, PALICC retained disease severity stratifications to help target prognosis and therapy. Interestingly, the data from Asia seem to support stepwise increases in mortality as a function of initial PARDS severity groups, while other data highlight major mortality differences between severe PARDS and all other PARDS patients. However, ventilator-free days and length of ventilation among survivors appear better calibrated with PARDS severity groupings. This may be the more important metric, as it is often difficult to understand how often children with PARDS die *from* PARDS (i.e., hypoxemia) or *with* PARDS (i.e., shock, neurologic injury). Additionally, it is clear that these severity groupings have different prognostic relevance at PARDS diagnosis compared to 6–48 hours after PARDS diagnosis. In fact, none of the ARDS definitions have mandated a delayed measure of ARDS severity, which may have important implications to gauge response to therapy, persistence of disease, and prognosis. These of course have to be balanced with the importance of early identification of patients who are likely to benefit from PARDS-specific therapies. Furthermore, these trajectories are also very clearly influenced by factors such as genetics, comorbidities, degree of inflammation, and therapies [67–69], which are not captured in the PARDS definition. As our diagnostic capabilities expand, it will be important to frequently reevaluate whether we can use other diagnostic tests, which better reflect the pathobiology of PARDS in our definitions.

## Conclusion

In conclusion, there are unique elements to the pathobiology of PARDS, which mandate a pediatric-specific definition. The PALICC group has created a pediatric-specific definition for ARDS, which was initially based on consensus opinion from established investigators in PARDS, with some validation using data from existing PARDS studies. Recent studies have provided some validation of this definition in a variety of international critical care settings. Furthermore, pediatric-specific evidence for therapeutic approaches are lacking in many important areas, but using the PALICC definition as a framework to better evaluate the risk-benefit profiles of individual therapies is important for both future investigations and clinical care of children with PARDS.

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