Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference

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

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Objectives: Although there are similarities in the pathophysiology of acute respiratory distress syndrome in adults and children, pediatric-specific practice patterns, comorbidities, and differences in outcome necessitate a pediatric-specific definition. We sought to create such a definition.

Design: A subgroup of pediatric acute respiratory distress syndrome investigators who drafted a pediatric-specific definition of acute respiratory distress syndrome based on consensus opinion and supported by detailed literature review tested elements of the definition with patient data from previously published investigations.

Settings: International PICUs.

Subjects: Children enrolled in published investigations of pediatric acute respiratory distress syndrome.

Interventions: None.

Measurements and Main Results: Several aspects of the proposed pediatric acute respiratory distress syndrome definition align with the Berlin Definition of acute respiratory distress syndrome in adults: timing of acute respiratory distress syndrome after a known risk factor, the potential for acute respiratory distress syndrome to coexist with left ventricular dysfunction, and

the importance of identifying a group of patients at risk to develop acute respiratory distress syndrome. There are insufficient data to support any specific age for "adult" acute respiratory distress syndrome compared with "pediatric" acute respiratory distress syndrome. However, children with perinatal-related respiratory failure should be excluded from the definition of pediatric acute respiratory distress syndrome. Larger departures from the Berlin Definition surround 1) simplification of chest imaging criteria to eliminate bilateral infiltrates; 2) use of pulse oximetry–based criteria when Pao_2 is unavailable; 3) inclusion of oxygenation index and oxygen saturation index instead of Pao_2/Fio_2 ratio with a minimum positive end-expiratory pressure level for invasively ventilated patients; 4) and specific inclusion of children with preexisting chronic lung disease or cyanotic congenital heart disease.

Conclusions: This pediatric-specific definition for acute respiratory distress syndrome builds on the adult-based Berlin Definition, but has been modified to account for differences between adults and children with acute respiratory distress syndrome. We propose using this definition for future investigations and clinical care of children with pediatric acute respiratory distress syndrome and encourage external validation with the hope for continued iterative refinement of the definition. (*Pediatr Crit Care Med* 2015; 16:S23–S40)

Key Words: epidemiology; lung injury; pediatric acute respiratory distress syndrome; pediatric intensive care units; respiratory insufficiency

In 1994, the American European Consensus Conference (AECC) defined acute respiratory distress syndrome (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 (1). For years, pediatric practitioners have used the AECC definition of ARDS for clinical care, research, and prognostication. Limitations of the AECC definition of ARDS have recently been addressed by the Berlin definition, but pediatric specific considerations were not included (2, 3). Although there are similarities in the pathophysiology of ARDS in adults and children, pediatric-specific practice patterns, comorbidities, and differences in outcome necessitate a pediatric-specific definition (4). We sought to create such a definition based on consensus opinion, validated with empirical data, when available.

MATERIALS AND METHODS

A group of pediatric critical care investigators were assembled to establish a pediatric-specific definition for ARDS. The group was tasked with determining whether the Berlin Criteria 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 (NRS) for acute hypoxemic respiratory failure (AHRF); 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 (LV) dysfunction are likely to be similar across a spectrum of age, but may need pediatric-specific modification.

Each of the above areas for consideration was formulated into Problem, Intervention, Comparison, and Outcome (PICO) questions, and detailed literature searches were performed to identify all relevant publications. Data from the literature search were used to justify conclusions for ultimate inclusion in the draft definition of pediatric ARDS (PARDS), arrived at via consensus from the small group. When existing published literature was sparse, secondary analysis of data from existing PARDS datasets were used to explore modification of the draft definition. These data were used to guide the definition.

Derivation Datasets

Two datasets were used as derivation sets to explore different aspects of the definition of PARDS when published literature was lacking. These represent secondary analyses of published data and are meant to help establish criteria for PARDS (5–7).

Validation Datasets

Cut points to classify PARDS severity were guided by data from the derivation sets and subsequently established by consensus. Secondary analysis of previously published data from members of the Pediatric Acute Lung Injury Consensus Conference (PALICC) group was aggregated to externally validate the proposed PARDS severity groups. Datasets were included if they had the required minimum data elements necessary to test the definition (5, 8–12).

RESULTS

Each of the areas above was formulated into PICO style questions. However, because of the nature of elements of the definition that we sought to test and the lack of clear comparative data, PICO questions did not yield robust literature search results. As a consequence, the investigators performed detailed literature searches related to specific aspects of the definition and reviewed all citations as well as their reference lists for relevant articles. The results of these searches are included where appropriate in the subsequent text. The definition is summarized in **Figures 1** and **2**. The sections below provide justification for the individual elements of the definition.

Incidence and Epidemiology

Population-based studies in the United States, Europe, Australia, and New Zealand using the AECC definition suggest that

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_2O [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.			

Figure 1. Pediatric acute respiratory distress syndrome (PARDS) definition. [1]Use Pao_2-based metric when available. If Pao_2 is not available, wean Fio_2 to maintain $Spo_2 \leq 97\%$ to calculate oxygen saturation index (OSI; [Fio_2 × mean airway pressure × 100]/Spo_2) or Spo_2:Fio_2 (SF) ratio. [2]For nonintubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation, see **Figure 2** for "at-risk" criteria. [3]Acute respiratory distress syndrome severity groups stratified by oxygenation index (OI; [Fio_2 × mean airway pressure × 100]/Pao_2) 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. CPAP = continuous positive airway pressure, PF = Pao_2:Fio_2.

the incidence of ARDS in adults ranges from 17.9 to 81.0 per 100,000 person-years (13–16). In contrast to adults, the incidence of ARDS in United States, European, Australian, and New Zealand children is 2.0–12.8 per 100,000 person-years (5, 9, 11, 17, 18). Although mortality from ARDS is lower in clinical trials, population-based studies suggest that the overall mortality of ARDS in adults is 27–45% (13–16, 19). ARDS attributable mortality in children appears to be lower than in adults (18–27%), although data from Australia suggest that pediatric and adult mortality from ARDS may be similar (35%) (8, 11, 18, 20, 21). Investigators from the King County Lung Injury Project (KCLIP, Washington) stratified the incidence and mortality of ARDS by age, but patients under 15 years were not included in the adult cohort (16). However, pediatric data from the same network of hospitals and patient catchment area support the conclusion that the incidence and mortality of ARDS is lowest in children and increases with advancing age (16, 18).

Most pediatric and adult studies report an increased incidence of ARDS in males versus females, but males do not seem to have increased mortality from ARDS (5, 8, 13–15, 18, 19, 22–24). Erickson et al (25) reported differences in the mortality of black and Hispanic compared with Caucasian PARDS patients, and it appears that the increased mortality of African American ARDS patients may be, in part, due to a common polymorphism of the Duffy minor blood group type (26). The percentage of pediatric and adult ARDS patients with preexisting illness appears to be similar (21–33% and 12–34%, respectively), but a number of studies report a higher incidence of preexisting illness in children (65–74%) (5, 11, 15, 18, 19, 23, 27, 28). Immunodeficiency is a common preexisting condition in both pediatric and adult patients that develop ARDS, and most studies show increased mortality among immunodeficient patients who develop ARDS (5, 13, 15, 18, 19, 22, 23). Although there may be differences in the type and severity of preexisting comorbidities, and there may be age-dependent differences in the risks of developing extrapulmonary organ failure, there are currently no validated scoring systems to make reliable comparisons between pediatric and adult patients. Age-dependent differences in etiology may contribute to differences in outcome between children and adults, but pneumonia, sepsis, aspiration, and trauma account for 63–92% of ARDS in both adults and children (5, 8, 11, 13, 16, 18, 19, 23). 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 (29, 30).

Age

There are intrinsic and extrinsic factors to age that may contribute to age-dependent differences in the incidence and mortality of PARDS. Extrinsic factors to age, such as the increased incidence of trauma in adolescent males, will be addressed in the section on comorbidities (31). Postnatal lung growth and development and innate and adaptive immune development are intrinsic to age and are likely to contribute to age-dependent differences in the incidence, mortality, and pathobiology of ARDS (32).

Postnatal lung growth and development is an important difference between children and adults with ARDS. Information about normal human lung morphogenesis is mostly extrapolated from animal studies (33–35). The major stages of postnatal lung development, alveolarization, microvascular maturation, and normal growth, occur simultaneously, but the peak rates at which each stage occurs are different. Human newborns have approximately 50 million alveoli, and postnatal alveolarization results in roughly 300 million alveoli in adults (36). Alveolarization may be nearly complete by 18 months of age, but it probably continues through attainment of adult height (35, 36). Microvascular maturation is characterized by a rapid increase in alveolar surface area, slowing of cell proliferation, decreased mesenchymal and interstitial tissue mass, and a change from the double alveolar capillary network in

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**
	Nasal mask CPAP or BiPAP	Oxygen via mask, nasal cannula or High Flow	Oxygen supplementation to maintain $SpO_2 \geq 88\%$ but OI < 4 or OSI < 5[1]
	$FiO_2 \geq 40\%$ to attain SpO_2 88-97%	SpO_2 88-97% with oxygen supplementation at minimum flow[2]: < 1 year: 2 L/min 1 – 5 years: 4 L/min 5 – 10 years: 6 L/min >10 years: 8 L/min	

Figure 2. At risk of pediatric acute respiratory distress syndrome (PARDS) definition. [1]If Pao_2 is not available, wean FIO_2 to maintain $Spo_2 \leq 97\%$ to calculate oxygen saturation index (OSI). [2]Given lack of available data, for patients on an oxygen blender, flow for at-risk calculation = FIO_2 × flow rate (L/min) (e.g., 6 L/min flow at 0.35 FIO_2 = 2.1 L/min). BiPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, OI = oxygenation index.

the newborn to the single capillary network in adulthood (36). Alveolar epithelial cell proliferation and differentiation, septation of alveoli, and increases in the luminal diameter of conducting airways continue until adult height is reached.

Several fundamental regulatory mechanisms of lung morphogenesis overlap with inflammatory, apoptotic, and repair mechanisms in the lungs. Fibroblast growth factors (FGF-7, FGF-10), nuclear factor κB, and transforming growth factor-β interactively regulate lung morphogenesis, innate immunity, coagulation, apoptosis, alveolar fluid clearance, and lung repair (37–39). Animal models of lung injury suggest age-dependent differences in transcriptional, inflammatory, injury, and repair responses to infectious stimuli and mechanical stretch (40–45). This is discussed in further detail in the Pathobiology article in this supplement (46).

Postnatal lung morphogenesis and immune development are likely to affect age-dependent differences in the incidence of infections as well as inflammatory and repair mechanisms in the lungs. In order to avoid confusion with lung injury that develops in premature infants or due to perinatal events or congenital abnormalities, a lower limit of age of PARDS was considered. The age at which the incidence of infant respiratory distress syndrome approaches zero cannot be determined from the literature. Although the pathobiology of acute lung injury (ALI) caused by perinatal events such as aspiration of meconium or group B Streptococcus may be similar to the diffuse inflammatory and injury mechanisms of ARDS, the unique pathophysiologies related to persistent fetal circulation, changes in perinatal pulmonary vascular resistance, and the processes of care by neonatologists compared with pediatric intensivists make it important to consider this group of patients separately. Finally, causes of AHRF due to congenital anomalies, for example, congenital diaphragmatic hernia, do not share the same pathobiology of ARDS and should be excluded. Therefore, although there are no data to support a lower limit of age of PARDS, exclusion criteria for PARDS should include causes of acute hypoxemia that are unique to the perinatal period, such as surfactant deficiency, lung injury from perinatal events, and congenital abnormalities.

In order to determine whether there should be an upper age limit of PARDS, methods to define a surrogate for completed lung morphogenesis (such as whether an individual has reached adult height) were considered. Population-based demographics cannot be used to determine when an individual has reached adult height. Determination of epiphyseal closure is the only reliable method to ascertain achievement of adult height in an individual patient, but this is not a reasonable criterion to include in the definition of PARDS. Therefore, the epidemiologic data of ARDS were explored to determine whether there is a clear breakpoint in the incidence or mortality of ARDS, sepsis, or pneumonia between adolescents and young adults. Data from the KCLIP do not suggest a clear breakpoint in the incidence or mortality of ARDS between adolescents and young adults (16, 18). Pneumonia and sepsis are the

TABLE 1. Center for Disease Control and Prevention Age-Adjusted Mortality per 100,000 Persons From Sepsis and Influenza and Pneumonia in the United States in 2009

Age (Yr)	Sepsis	Influenza and Pneumonia
< 1	5.2	5.9
1–4	0.4	0.9
5–14	0.2	0.6
15–24	0.3	1
25–34	0.9	1.9
35–44	2.2	3.2
45–54	5.5	6.5
55–64	13.3	11.9
65–74	32	30.1
75–84	78.4	105.9
≥ 85	173.8	413.5

most commonly identified etiologies of ARDS in children and adults. In the United States, the Center for Disease Control and Prevention reports that mortality from pneumonia, viral respiratory infections, and sepsis decreases from infancy to a nadir in 5- to 14-year-old children and then increases to a peak in the elderly (47) (**Table 1**). The World Health Organization (WHO) (48) provides mortality data from lower respiratory tract infections stratified by age, but it does not provide data on mortality from sepsis. These global data also suggest that mortality from respiratory tract infections decreases from infancy to a nadir through adolescence and young adulthood and begins to increase in 45- to 59-year-old persons (49). However, WHO data also suggest that regional and income differences have a more significant effect on mortality from pneumonia than age, making global comparisons difficult. Therefore, there does not appear to be a clear breakpoint in the incidence or mortality of ARDS, sepsis, or pneumonia between adolescents and young adults. Finally, there is no clear breakpoint at which children are no longer cared for by pediatricians. Increasingly, there are patients in their 20s 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, healthcare providers caring for adolescents and young adults should use the definition of ARDS with which he/she is most familiar.

Recommendations:

There are age-related differences in the epidemiology and risk factors of PARDS, and there are likely age-dependent differences in the pathobiology of PARDS. However, there are no data to suggest population-wide age-based criteria for the definition of PARDS.

1.1.1 We recommend that there should not be age criteria for the definition of PARDS. However, exclusion criteria for PARDS should include causes of acute hypoxemia that are unique to the perinatal period, such as prematurity-related lung disease, perinatal lung injury (e.g., meconium aspiration syndrome and pneumonia and sepsis acquired during delivery), or other congenital abnormalities (e.g., congenital diaphragmatic hernia or alveolar capillary dysplasia). *Strong agreement*

1.1.2 We recommend that, in the absence of a compelling rationale related to physiology or feasibility, studies of PARDS should not include age limits. In order to better understand the pathobiology of PARDS across the spectrum of age, and in the absence of a clear breakpoint in the epidemiology of PARDS, adult and pediatric investigators should engage in collaborative studies targeting adolescents and young adults. Future studies are needed to evaluate potential age-dependent differences in the pathophysiology of PARDS across the entire pediatric age spectrum. *Strong agreement*

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 (1, 3). Discussion in the latter article noted that most patients with ARDS are identified within 72 hours of an underlying risk factor, and nearly all patients with ARDS are identified within 7 days.

An adult study in 1995 that enrolled 182 subjects investigated the onset of ARDS secondary to sepsis, trauma, drug overdose, and aspiration (50). Of patients who developed ARDS following sepsis, 32% developed ARDS in less than 12 hours and 54% by 24 hours. Of those who developed ARDS following trauma, 16% developed ARDS in less than 12 hours and 29% by 24 hours. Of those who developed ARDS following overdose or aspiration, 31% developed ARDS in less than 12 hours and 38% by 24 hours. All subjects developed ARDS within 7 days of their initial insult. In another study of 168 adult patients with ALI from three Australian states, the percentage of patients fulfilling AECC ALI criteria at 24 hours, 48 hours, 72 hours, and 7 days from the time of ICU admission were 78%, 88%, 94%, and 98%, respectively (13). A prospective 10-week national audit for ARDS was conducted among 14 adult ICUs in Ireland during 2006. ALI/ARDS was diagnosed in 196 patients (78%) at the time of ICU admission and another 55 (22%) developed ALI/ARDS following ICU admission (51).

More than half of adults with septic shock develop ARDS, the most common comorbidity associated with sepsis. In an adult cohort of 160 patients with septic shock, 71 (44%) developed ALI at a median of 5 hours (range, 2–94 hr) after the onset of septic shock (52). Ninety percent of patients developed ALI during the first 12 hours of septic shock.

In a recent study conducted by the U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators, 377 adults (from a screened cohort of 5,992 patients) developed ALI at a median of 2 days with an interquartile range of 1–4 days following admission to the hospital, and 229 (61%) of these also met the AECC definition for ARDS (53). Accordingly, if 75% of patients demonstrated ALI within 4 days, nearly 100% would be expected to have demonstrated ARDS by day 7. Another recent population-based retrospective cohort study examined cases of ARDS among Olmsted County citizens hospitalized at the Mayo Clinic in Rochester, MN, during 2006 (54). Thirty-nine patients (33%) exhibited evidence of ARDS at hospital admission. Another 79 patients (67%) developed ARDS after hospitalization with a median time to ARDS after admission of 30 hours (interquartile range, 10–82 hr). Essentially, the entire cohort exhibited ARDS by 7 days following hospitalization, the vast majority by 3 days.

In a study of 44 mechanically ventilated children, ages 0–18, with ALI, from The Netherlands, 35 (79.5%) developed ARDS (21). About half fulfilled the ARDS criteria at PICU admission and another 25% later in the course of their illness, but timing details of the latter cohort are not provided. In another study of PARDS in China, 105 children who were 1–14 years old developed ARDS with median and 95th percentile times from

the onset of acute insult to the onset of ARDS of 72 hours and 168 hours (7 d), respectively (28).

Some subgroups of patients develop ARDS very quickly. For example, acute transfusion-related ALI is defined as ARDS that develops within 6 hours of a transfusion (55, 56). Similarly, neurogenic pulmonary edema develops rapidly following intracranial insult, typically from traumatic brain injury or subarachnoid hemorrhage (57). Likewise, ARDS usually develops promptly in the setting of pediatric drowning-related lung injury (58).

In summary, ARDS most commonly presents at the time of hospital/ICU admission with the remainder of cases identified within the first week following admission. Although pediatric studies are few, data obtained from children supports this same conclusion.

Recommendation:

1.2.1 We recommend that symptoms of hypoxemia and radiographic changes must occur within 7 days of a known clinical insult to qualify for PARDS. *Strong agreement*

Coexistence of ARDS With LV Failure/Dysfunction

The issue of LV dysfunction/failure is specifically addressed by both the AECC criteria and the Berlin criteria. In the original AECC criteria, the presence of left atrial hypertension (pulmonary artery occlusion pressure > 18 mm Hg or clinical evidence of left atrial hypertension) is an exclusion criterion. In the Berlin criteria, this exclusion criterion has been changed to cases only where the respiratory failure is not fully explained by cardiac failure or fluid overload. There are logical reasons for this change:

1. Pulmonary artery catheterization is not as frequently performed in adult critical care management. In pediatric critical care, pulmonary artery catheterization is rarely practiced. It is recommended in the Berlin criteria that if there are no clear risk factors for ARDS, then objective assessment to exclude cardiac failure (echocardiography) should be performed.
2. It is implied from the Berlin criteria that some degree of cardiac failure/dysfunction may coexist with ARDS, while not specifically being the primary cause.
3. Varying degrees of LV dysfunction are frequently reported in children with ARDS. LV dysfunction is frequently seen as a sequela of ARDS but may be coexistent with ARDS. LV dysfunction has been shown to be associated with increased mortality from ARDS in children (5, 8).

The definition of LV failure is not specified in the Berlin definition. Echocardiography is widely used in pediatrics to quantify ventricular function and is a good predictor of cardiac symptoms and outcomes in children with LV failure (59). Assessment of LV function includes assessment of cardiac output (aortic Doppler flow velocities), systolic function (shortening fraction and ejection fraction), and diastolic function (mitral valve inflow techniques).

The accepted normal range for aortic peak flow velocity is 72–120 cm/s (mean, 92 cm/s) and velocity-time integral (60) is 12.6–22.5 cm (mean, 15.7 cm) (61). The accepted normal ranges for LV shortening fraction is 28–45% (95% CI) and for LV ejection fraction is 64–83% (95% CI) (62). Mitral valve inflow techniques include isovolumic relaxation time (normal, 71 ± 14 ms) (63) and peak E-wave velocity (normal, 0.60–0.68 m/s) (64).

Recommendation:

1.3.1 We recommend that children with LV heart dysfunction that fulfill all other PARDS criteria have PARDS if the acute hypoxemia and new chest imaging changes cannot be explained by acute LV heart failure or fluid overload. *Strong agreement*

Radiographic Findings in PARDS

Both AECC and Berlin definitions of ARDS require the presence of bilateral pulmonary infiltrates on chest radiograph (CXR). The intent of the inclusion of radiographic criteria in the definition of ARDS is to identify patients who have the unique pathobiology of ARDS, initially described histopathologically from autopsy (65). As has been recently demonstrated, the clinical syndrome of ARDS does not always translate to the histologic appearance of diffuse alveolar damag (66). While the Berlin Definition of ARDS in adults has high sensitivity in detecting diffuse alveolar damage at autopsy, the specificity is only 30–40%. 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 diffuse inflammatory processes seen in both lungs, but it is unclear whether 1) the CXR sensitivity is enough to detect all pulmonary parenchymal inflammation and edema; 2) findings consistent with pulmonary parenchymal inflammation and edema need to be radiographically apparent in both lungs; and 3) the presence of bilateral infiltrates on CXR imparts additional risk of poor outcome not otherwise captured with other elements of the definition of ARDS, such as the degree of hypoxemia.

These considerations are particularly important because if CXR findings are retained for the definition of PARDS, there is large interobserver variability in the interpretation of the CXRs. It is unclear if this can be minimized in pediatrics by common training, as proposed by the Berlin definition of ARDS in adults (67–69).

1. Sensitivity of CXR. The utility of plain frontal CXR in the ICU has long been a subject of debate. Several studies have demonstrated the utility of CXR in determining positions of catheters and tubes and detection of abnormalities that may require an intervention, such as a pneumothorax or pleural or pericardial effusion (70–73). Multiple investigators have shown low sensitivity of CXR to detect subtle changes in consolidation, atelectasis, and edema, although protocolized and standardized interpretations may have prognostic implications (72, 74, 75). Furthermore, the presence of pulmonary infiltrates on CXR in ARDS frequently lags behind the development of hypoxemia (76, 77), and almost all biomarker studies in pediatric and adult ARDS demonstrate that the pathophysiologic processes of inflammation, endothelial injury, coagulopathy, etc. are active with the "traditional" onset of ARDS (Pa_{O_2}:F_{IO_2} [PF] ratio < 300 and bilateral infiltrates), implying the processes started before we clinically identify the patient. For this reason, the AECC definition of ARDS allowed for minor bilateral

changes to the CXR, which may contribute to the interobserver variability in their interpretation (1). Furthermore, chest CT has demonstrated poor correlation between areas in the lung that appear consolidated on CXR with relatively normal-appearing areas of lung on CT (78–81). Conversely, traumatic lung contusions visible on CT may not be seen on frontal CXRs (82). Overall, the sensitivity of CXR for detecting areas of alveolar consolidation compared to CT in adults with ARDS is between 60% and 70% (74). Even further, there is evidence to suggest that CT inadequately represents areas of metabolic activity and inflammation. Adult studies have confirmed that areas of lung inflammation identified on PET scan may not be consolidated on CT (83). The risks of transporting unstable ARDS patients to CT scan have led to the use of ultrasonography to determine the extent and distribution of lung edema in patients with lung injury, with some evidence to support that lung ultrasonography correlates well with CT scan findings, and is superior to clinical examination and frontal chest radiography (74). However, lung ultrasonography requires more specialized training for standardized interpretation and may not be available routinely. Perhaps as a consequence of the requirement of bilateral infiltrates for the definition of ARDS, we could identify no studies investigating the frequency with which patients do not have bilateral infiltrates on CXR but have other radiographic evidence of ARDS.

2. There is debate as to whether the pathophysiology that occurs with ARDS can be present in patients with severe unilateral disease. In fact, in the discussion of the AECC definition, there was not agreement on whether the presence of bilateral infiltrates should be included in the definition, with some investigators arguing that severe unilateral disease should be included in the definition of ARDS (13). Furthermore, it is clear that despite the presence of bilateral infiltrates on CXR, the distribution of diseased lung in ARDS is inhomogeneous (above). Given these findings, some management strategies may be relevant and applicable for all cases of AHRF, whereas some may be useful only for those with certain pathophysiologic findings. For example, the choice of positive end-expiratory pressure (PEEP) may differ based on whether someone has homogeneous disease in both lungs, nonhomogeneous disease in both lungs, or homogeneous disease in one lung with relative preservation of normal mechanics in the other lung. The degree of recruitable lung may be a function of the mechanism of lung injury and the regional distribution of lung disease. As such, specific treatment recommendations or management strategies may not even be applicable to all patients who meet diagnostic criteria with bilateral pulmonary infiltrates.
3. Finally, it is not clear whether the presence of bilateral pulmonary infiltrates helps with risk stratification for children with hypoxemic respiratory failure, that is, does it capture additional risk to the degree of oxygenation impairment? Two studies from Scandinavian countries demonstrate similar mortality for adult patients with AHRF, ALI, and ARDS and that the presence of bilateral infiltrates provides minimal predictive value for outcome (15, 84). This is in contrast to a study from France, which showed higher mortality for adults with bilateral infiltrates on frontal CXR, with similar degrees of hypoxemia, and without significant LV dysfunction (85). Although mortality rates were significantly higher with bilateral infiltrates (60% vs 40%), after controlling for patient demographics and initial severity of illness, the presence of bilateral infiltrates had no association with mortality. As such, while there may be some association between bilateral infiltrates and outcome, it is not a robust predictor of mortality in adults with respiratory failure.

There are few pediatric studies that examined the association of bilateral infiltrates with outcome. Two observational studies in China demonstrated slightly higher mortality for patients with ARDS (PF ratio < 200 and bilateral infiltrates on CXR) compared with AHRF (PF < 300 without bilateral infiltrates) (27, 86). However, whether the increased risk of mortality in the ARDS group was a function of worse hypoxemia or bilateral infiltrates was not determined. Therefore, we used previously published data from the Children's Hospital of Los Angeles (CHLA) to explore whether bilateral infiltrates on CXR contributed to PARDS mortality (6). Patients with AHRF ($n = 397$) were analyzed for the presence of bilateral pulmonary infiltrates on CXR ($n = 192$). The mortality for children with bilateral pulmonary infiltrates was 22.9% compared with 17.6% for those without bilateral infiltrates ($p = 0.2$). However, in patients with mild hypoxemia (PF, 200–300 or oxygenation index [OI], 4–8), there was a nonstatistically significant difference ($p = 0.2$) in mortality between patients with and without bilateral infiltrates (12.8% vs 6.4% with PF ratio 200–300 or 13% vs 8% with OI 4–8; **Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A161; and **Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A162). In pediatric patients with more severe hypoxemia (PF < 200 or OI > 8), the mortality rate was nearly identical between those with and without bilateral infiltrates (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A161; and Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/PCC/A162).

The intent of including bilateral infiltrates on chest radiography in the definition of ARDS was to distinguish the unique pathophysiology of ARDS from conditions such as lobar pneumonia. Unfortunately, the low sensitivity and the problem of interobserver variability of applying this definition criterion may be contributing to underrecognition of ARDS. Furthermore, it appears as if the radiologic presence of bilateral infiltrates adds little over the degree of hypoxemia in characterizing risk for poor outcome. For these reasons, we advocate removal of the requirement of bilateral infiltrates from the definition of PARDS. We have elected not to eliminate radiology altogether from the definition to help differentiate other causes of AHRF that 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. To minimize variability, investigators should initiate standardized interpretation of all CXRs. Although it may not be feasible to require single practitioner interpretation for all types of investigations, investigators must minimize interobserver variability in the interpretation of chest imaging in any study of PARDS. Future study is needed regarding whether adequate common training can reduce interobserver variability in CXR interpretation in PARDS, as has been suggested in the Berlin Definition of ARDS.

Recommendations:

1.4.1 We recommend that chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease are necessary to diagnose PARDS. *Strong agreement*

1.4.2 We recommend that future clinical trials for PARDS should stratify patients by the presence or absence of bilateral infiltrates on chest imaging. In order to minimize variability in these studies, investigators should standardize interpretation of all chest imaging. *Strong agreement*

1.4.3 We recommend that future studies are needed to determine the optimal common training or effect of automated methodologies to reduce interobserver variability in the interpretation of chest imaging for PARDS. *Strong agreement*

Respiratory Criteria for Disease Severity

Several pediatric investigators have examined the association of hypoxemia and outcome for PARDS, demonstrating that composite markers such as PF, Sp_{O_2}:F_{IO_2} (SF), OI, oxygen saturation index (OSI), and Lung Injury Score are associated with outcome for children with ARDS (6–8, 87–90). Most studies have demonstrated relatively similar discriminatory ability for these metrics. However, unanswered questions surround whether 1) minimal or standardized ventilatory support is necessary for accurate risk stratification, given changes to PF or SF ratios in response to ventilator management and 2) the timing of the assessment of hypoxemia affects the association with outcome. Finally, it is unclear whether other respiratory-specific characteristics of lung injured patients such as dead space or pulmonary compliance can help with risk stratification.

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 continuous positive airway pressure (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 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 acute respiratory distress syndrome network (ARDSNet) studies (2, 3). When looking at PEEP management in ARDSNet centers, even before enrollment in clinical trials, the mean PEEP for patients ranged from 8.4 to 9.5 cm H_2O, and 50% of patients had a baseline PEEP greater than 10 cm H_2O (91). Furthermore, once enrolled in the ARDSNet trials, PEEP is managed in a protocolized fashion, using a PEEP/F_{IO_2} titration table (92). This has led to the conclusion that PEEP has minimal effect on outcome for adults managed with ARDSNet protocols, and F_{IO_2} imparts the most risk. Given that PEEP and F_{IO_2} are changed in a protocolized fashion in concert, there is significant colinearity between these variables, making it difficult to truly determine which variable imparts the most risk. Three observational cohort studies have demonstrated that pediatric intensivists use less PEEP than their adult colleagues, with average PEEP between 5 and 7 cm H_2O, and over 50% of PARDS patients are treated with PEEP less than or equal to 5 cm H_2O (6, 8, 23). Furthermore, two studies in children have demonstrated significant variability in the use of PEEP among practitioners with a poor relationship between PEEP and F_{IO_2} and an overall reluctance to increase PEEP beyond 10 cm H_2O (23, 93). As such, conclusions from ARDSNet studies regarding the minimal impact of PEEP on outcome over hypoxemia (measured by PF ratio) cannot be applied to pediatrics, given major differences in PEEP management.

Variability in ventilator management and how it affects PF ratios have been addressed by some pediatric investigators using specific respiratory maneuvers to define PARDS, such as calculating PF when the patient is on a minimum PEEP of 10 cm H_2O and F_{IO_2} of 0.5 after 24 hours of mechanical ventilation (11). While such a maneuver may facilitate risk stratification, requiring specific ventilator manipulations may impair recognition of PARDS by clinicians because it relies upon the clinician to suspect the patient may have PARDS and then to perform the maneuver to determine whether the patient meets diagnostic criteria. In order for future epidemiologic investigations of PARDS to detect the true incidence of PARDS, the definition must not depend on clinician suspicion and performance of specific maneuvers that are not part of routine care. Therefore, we sought to determine whether risk could be determined without requiring specific respiratory maneuvers. Furthermore, we wanted to avoid using PEEP in the diagnostic criteria because PEEP is unavailable for patients on high-frequency oscillatory ventilation (HFOV), which is commonly used for PARDS. We wanted risk categories to have meaningful clinical value, rather than be convenient cut points that are easy to remember. Given the issues discussed above regarding PF ratio and ventilatory support and the common use of HFOV, we elected to use OI ($[F_{IO_2} \times \text{Mean airway pressure} \times 100] \div Pa_{O_2}$) to define severity of PARDS. Initially, we used OI cut points that have been described in the literature for clinical decision making. These include OI less than 6 (considered for extubation readiness), greater than or equal to 13 (considered for more severe lung injury in surfactant trials), and greater than 20 for consideration of HFOV (10, 88, 94). These cut points were validated using two datasets (CHLA and Australia New Zealand Intensive Care Society [ANZICS]) (5, 6). We found stepwise increases in mortality between each group, but very few patients had an OI between 13 and 20. Data from the ANZICS group also suggested that there was no discriminatory value between an OI less than 6 and 6–13 with mortality between 14% and 16% in these groups (**Table 2**).

TABLE 2. Distribution of Patients and Mortality Based on Oxygenation Index Cut Points Drawn From the Literature

Studies	Oxygenation Index				Total
	> 20	13–20	6–13	< 6	
Khemani et al (6) (%)					
No. of patients	76 (19.1)	51 (12.8)	138 (34.7)	132 (33.2)	397
Mortality	33 (43.4)	12 (23.5)	23 (16.7)	12 (9.1)	80 (20.2)
Erickson et al (5) (%)					
No. of patients	32 (28.1)	16 (14.0)	31 (27.2)	35 (30.7)	114
Mortality	18 (56.3)	7 (43.8)	5 (16.1)	5 (14.3)	35 (30.7)

Data from two published studies on pediatric lung injury.

For these reasons, we looked at the data for natural cut points. Analysis of the CHLA dataset demonstrated clearer mortality groups (**Fig. 3**). The risk of death nearly doubled for each successive cut point: OI less than 4 (at risk for PARDS), 4–8 (mild PARDS), 8–16 (moderate PARDS), and greater than 16 (severe PARDS) with a relatively equal distribution of patients within the mild, moderate, and severe groups. The OI less than 4 group was identified as an at-risk group, as the mortality was extremely low (4% CHLA). To test these cut points, data were aggregated from six other published studies of PARDS (**Table 3**). Although there were slight differences between each study, when aggregated, mortality increased stepwise with each of the groups, with roughly a third of the patients in the mild, moderate, and severe groups, respectively (Table 3). We thought it important to stratify risk into different ranges, as this will facilitate common definitions for future research and therapies targeting children with different degrees of lung injury. Given clear differences in mortality and outcome based on disease severity, as well as potential differences in pathophysiology, risk benefit profiles may differ based on disease severity (94, 95).

In order to address issues related to timing of the diagnosis, we sought to determine whether timing of the PF ratio or OI discriminated risk of mortality. Several pediatric investigators have demonstrated stronger associations with OI and mortality for each day the patient remains on mechanical ventilation (6, 87). The PF ratio can be affected by ventilator management, and it has been shown to have higher predictive ability for initial values compared with values from subsequent days of mechanical ventilation (6). In order to account for ventilator management, we sought to compare OI with PF ratio using the initial value after intubation and mechanical ventilation and the worst value within the first 3 days of mechanical ventilation. We felt that this was important because patients may not stay within their initially assigned risk group throughout the course of mechanical ventilation. Studies that wish to enroll patients only with moderate or severe lung injury may enroll patients 2–3 days into their mechanical ventilation course. Given these variables may change based on both disease progression and ventilator management, we sought to see if there was a difference in discrimination between PF ratio and OI over time.

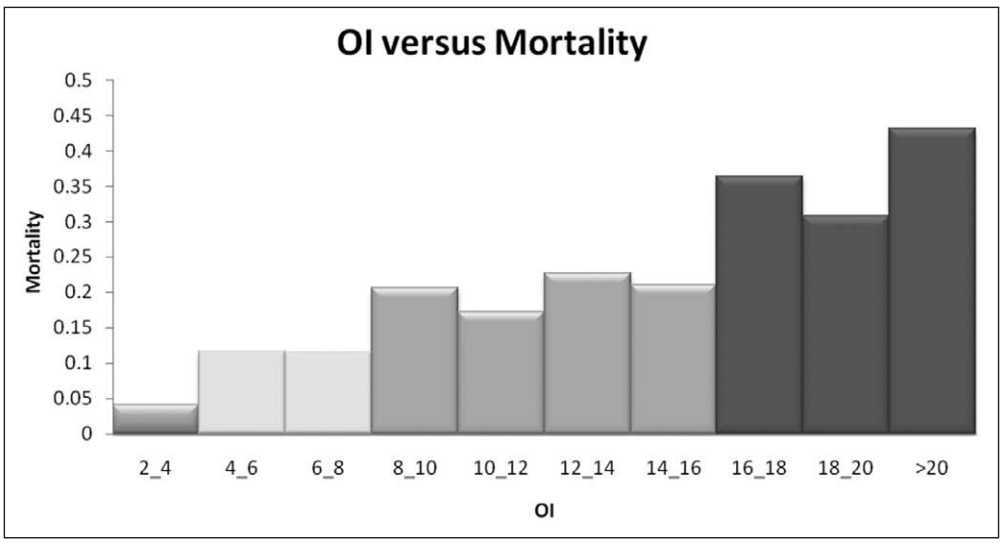

Figure 3. Distribution of initial oxygenation index (OI) and mortality from Children's Hospital of Los Angeles dataset (Khemani et al [6]) ($n = 397$). Mortality increases as OI increases, but there appear to be clear groups where mortality steps up (OI, < 4, 4–8, 8–16, and > 16).

Combining the two datasets (511 patients), it appears that many patients move from less to more severe lung injury during the first few days of mechanical ventilation (**Tables 4** and **5** and **Figs. 4** and **5**). The area under the curve (AUC) for the initial PF ratio when compared with the worst PF in the first 3 days of mechanical ventilation to discriminate mortality were both near 0.71. However, for OI, the AUC for the baseline value was 0.72 and increased marginally to 0.75 when considering the worst value within the first 3 days of mechanical ventilation. These data suggest that OI may have

TABLE 3. Distribution of Patients and Mortality Based on Oxygenation Index Cut Points Derived From the Children's Hospital of Los Angeles Dataset and Validated With Six Other Pediatric Studies

Studies	Oxygenation Index				Total
	> 16 (Severe)	8–16 (Moderate)	4–8 (Mild)	< 4 (At Risk)	
Derivation set (%)					
Khemani et al (6)					
Number	98 (24.7)	104 (26.2)	147 (37.1)	48 (12.1)	397
Mortality	40 (40.8)	21 (20.2)	23 (11.6)	2 (4.2)	80 (20.2)
Validation set (%)					
Flori et al (8)					
Number	28 (16.4)	60 (35.1)	67 (39.2)	16 (9.4)	171
Mortality	10 (35.5)	16 (26.7)	13 (19.4)	1 (6.25)	40 (23.4)
Curley et al (10)					
Number	34 (40)	28 (33)	20 (24)	3 (3)	85
Mortality	2 (5.9)	4 (14.3)	1 (5)	0 (0)	7 (8.2)
Erickson et al (5)					
Number	38 (33.3)	31 (27.2)	36 (31.6)	9 (7.9)	114
Mortality	20 (52.6)	10 (32.3)	5 (13.9)	0 (0)	35 (30.7)
Kneyber et al (9)					
Number	8 (27.6)	11 (37.9)	10 (34.5)	0 (0)	29
Mortality	1 (12.5)	3 (27.3)	1 (10)	0 (0)	5 (17.3)
López-Fernández (11)					
Number	72 (55)	47 (35.9)	12 (9.1)	0 (0)	131
Mortality	24 (33.3)	10 (21.3)	3 (25)	0(0)	37 (28.2)
Sapru et al (12)					
Number	47 (28)	68 (40.2)	40 (23.7)	14 (8.3)	169
Mortality	9 (19.1)	11 (16.2)	0 (0)	0 (0)	20 (11.9)
Validation set total (%)					
Number	225 (32.7)	241 (34.8)	184 (26.6)	42 (6.1)	692
Mortality	66 (29.3)	54 (22.4)	23 (12.5)	1 (2.4)	144 (20.8)

better discriminatory value for mortality than PF ratio, and the relationship between OI and mortality strengthens as the patient remains on mechanical ventilation for the first 3 days (6). The AUC of the worst OI and mortality is statistically significantly higher than the AUC of the worst PF ratio and mortality ($p = 0.02$). All other comparisons are not statistically significantly different (**Table 6**).

Recommendations:

1.5.1 We recommend that OI, in preference to PF ratio, should be the primary metric of lung disease severity to define PARDS for all patients treated with invasive mechanical ventilation. *Strong agreement*

1.5.2 We recommend that PF ratio should be used to diagnose PARDS for patients receiving noninvasive, full face mask ventilation (CPAP or bilevel positive airway pressure [BiPAP]) with a minimum CPAP of 5 cm H_2O. *Strong agreement*

Pulse Oximetry Versus Pao_2

Fewer arterial blood gases are obtained in PICUs compared with adult units, and the use of NRS has resulted in increasing number of patients with lung injury that are cared for outside of ICUs (10, 23, 96, 97). Therefore, it is imperative to create a definition for PARDS that does not rely on the subjective decision to obtain an arterial blood gas (9). Given the strong linear relationship between OSI ($[Fio_2 \times \text{Mean airway pressure} \times 100]/Spo_2$) and OI

TABLE 4. Distrubution of Patients and Mortality Based on Initial and Worst Pao_2:FIo_2 Ratio in the First 3 Days of Mechancial Ventilation

	Pao_2:FIo_2 Ratio			
Timing	< 100	100–200	200–300	Total
Baseline (first) (%)				
n	173 (33.9)	221 (43.3)	117 (21.6)	511
Mortality	69 (39.9)	35 (15.8)	11 (9.4)	115 (22.5)
Worst value 3 days (%)				
n	210 (37.5)	230 (46.9)	71 (15.6)	511
Mortality	75 (35.7)	35 (15.2)	5 (7)	115 (22.5)

Data from both Children's Hospital of Los Angeles (6) and Australia New Zealand Intensive Care Society (5) studies combined.

TABLE 5. Distrubution of Patients and Mortality Based on Initial and Worst Oxygenation Index in the First 3 Days of Mechancial Ventilation

	Oxygenation Index				
Timing	> 16	8–16	4–8	< 4	Total
Baseline (first) (%)					
n	137 (26.8)	135 (26.4)	183 (35.8)	56 (11.0)	511
Mortality	60 (43.8)	31 (23)	22 (12.0)	2 (3.6)	115 (22.5)
Worst value 3 days (%)					
n	180 (35.2)	140 (27.4)	156 (30.5)	35 (6.8)	511
Mortality	73 (40.6)	29 (20.7)	12 (7.7)	1 (2.9)	115 (22.5)

Data from both Children's Hospital of Los Angeles (6) and Australia New Zealand Intensive Care Society (5) studies combined.

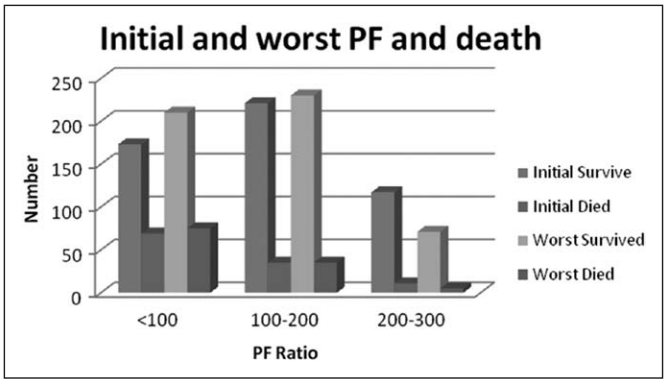

Figure 4. Initial and worst Pao_2:FIo_2 (PF) ratio in the first 3 days of mechanical ventilation. Distribution of survivors and nonsurvivors. Note that the moderate and severe hypoxemia groups have more patients over time, indicating that several patients have worsening lung disease severity in the first 3 days of mechanical ventilation.

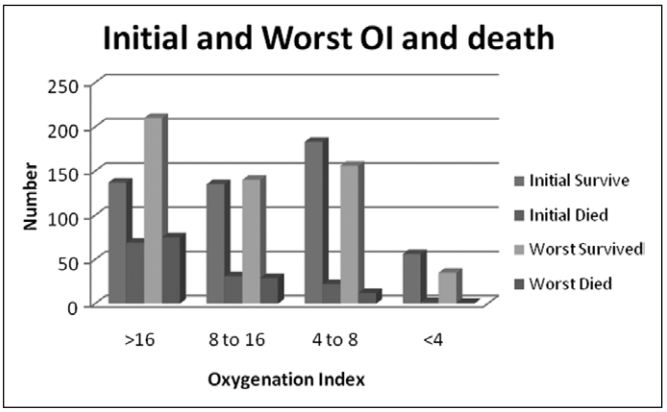

Figure 5. Initial and worst oxygenation index (OI) in the first 3 days of mechanical ventilation. Distribution of survivors and nonsurvivors. Similar to Pao_2:FIo_2 ratio shown in Figure 4, the moderate (OI, 8–16) and severe (OI > 16) hypoxemia groups have more patients over time, indicating that several patients have worsening lung disease severity in the first 3 days of mechanical ventilation.

when the Spo_2 is less than or equal to 97%, we have established OSI cut points to correspond with the OI cut points proposed above (88) (Fig. 1). The SF ratio also has a strong relationship with PF ratio, and as a screening tool, the use of an SF ratio has moderate positive likelihood ratios to identify patients with PF ratios less than 300 or less than 200, but very high posttest probability for patients who are invasively ventilated (88, 89, 98). As such, if a mechanically ventilated patient meets SF criteria, he or she will very likely meet PF criteria, allowing for its use for consideration for inclusion in a clinical trial. It may not, however, fully capture all patients that may meet PF criteria of less than 300, and therefore may not be adequate for all

TABLE 6. Area Under the Curve of the Receiver Operating Plots for Initial and Worst Values of Pao_2:FIO_2 Ratio and Oxygenation Index on Mortality

Criterion	Area Under the Curve	95% CI
Initial PF ratio	0.707	0.652–0.761
Initial OI	0.723	0.668–0.776
Worst PF 3 d	0.715	0.662–0.769
Worst OI 3 d	0.747	0.697–0.797

PF = Pao_2:FIO_2, OI = oxygenation index.
Data from both Children's Hospital of Los Angeles (6) and Australia New Zealand Intensive Care Society (5) studies combined.

epidemiologic studies. It is unclear how well SF ratio performs in relation to PF ratio for children receiving noninvasive ventilation, given difficulties in calculating FIO_2, and the potential effect modification based on the degree of ventilatory support. For this reason, we do not recommend applying SF ratios for nonintubated patients (or those not on full face mask noninvasive ventilation) to grade severity, but rather creating guidelines based on combinations of SpO_2 and minimal delivered oxygen to establish who is at risk for PARDS (see below).

Recommendation:

1.6.1 We recommend that OSI should be used when an OI is not available for stratification of risk for patients receiving invasive mechanical ventilation. *Strong agreement*

1.6.2 We recommend that oxygen saturation SF ratio can be used when PF ratio is not available to diagnose PARDS in patients receiving noninvasive full-face mask ventilation (CPAP or BiPAP) with a minimum CPAP of 5cm H_2O. *Strong agreement*

Dead Space

Next, we sought to explore whether a measure of dead space would be relevant for further risk stratification. Volumetric capnography remains the most accepted way to measure dead space, but there are no studies examining the association between volumetric capnography and mortality in PARDS. In a study by Ghuman et al (7), alveolar dead space fraction (AVDSF) combined with OSI was shown to have a nonstatistically significant increase in risk stratification of mortality when compared with OSI alone for children with ARDS. Secondary analysis of that dataset is shown in the **electronic supplement** (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/A163; **Supplemental Table 4**, Supplemental Digital Content 4, http://links.lww.com/PCC/A164). Patients with AVDSF greater than 0.23 had an overall mortality of 46%, whereas mortality was 13% in patients with AVDSF less than or equal to 0.23. AVDSF appears to add to the predictive ability regardless of the degree of hypoxemia, whether stratified by PF ratio or OI. Because these are limited data from a small sample and a single center, there is insufficient evidence to recommend a measure of dead space in the definition of PARDS. However, it appears that increased dead space (as measured by AVDSF) may be useful for additional risk stratification in clinical trials for children with PARDS, and further study is warranted. Furthermore, the combination of severe hypoxemia and elevated dead space may represent a particularly high-risk group, with mortality of over 50%. Given difficulties in accurate measurement of tidal volume in children (see below), we elected not to consider corrected minute ventilation, in defining PARDS.

Recommendations:

1.7.1 We recommend that, given the limited published data on dead space in PARDS, there is insufficient evidence to recommend a measure of dead space as part of the diagnostic criteria for PARDS. *Strong agreement*

1.7.2 We recommend that future study is needed to determine the potential relevance of elevated dead space for the definition of PARDS. *Strong agreement*

Respiratory System Compliance

Several unique issues for measurement of tidal volume in children limit the applicability of measurements of respiratory system compliance. Tidal volume cannot be calculated accurately if: 1) there is a significant air leak around the endotracheal tube, a problem that may be minimized in patients with severe ARDS as most will have cuffed endotracheal tubes; 2) the measurement of ideal body weight is more complicated in children, particularly those with severe scoliosis in which an accurate measurement of height to calculate predicted body weight is difficult; and 3) the device and location of the device (proximal airway vs at the ventilator) to measure tidal volume may result in different values for tidal volume, based on the type of ventilator, circuit tubing used, compliance of the patient, compliance of the tubing, and size of the patient (96). For these reasons, we have elected to omit compliance from the definition of PARDS. It may be used for study-specific risk stratification, with detailed instruction and standardization of measurements.

Recommendations:

1.7.3 We recommend that measures of respiratory system compliance should not be used for the definition of PARDS. Future studies of respiratory system compliance with reliable and standardized methods for measurement are warranted to determine the relevance of respiratory system compliance to the diagnosis and risk stratification of PARDS. *Strong agreement*

Characterizing Oxygen Delivery for NRS

NRS is being used with increasing frequency for acute respiratory failure in adult ICUs and PICUs (see section on noninvasive ventilation [99]), and there are an increasing number of patient interfaces available. Nasal modes of NRS allow for entrainment of room air during inspiration, making calculation of SF or PF ratios difficult. In order to determine the incidence of ARDS in adults and children by capturing patients cared for out of ICUs where suspicion of ARDS may be low, NRS is common, and arterial blood sampling is uncommon, an estimation of FIO_2 is necessary for calculation of SF ratio (9, 96, 97). Conventional methods of estimating the fraction of delivered oxygen (FdO_2) 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 F_{IO_2} by the American Association of Respiratory Care suggest that regular nasal cannula do not provide an F_{IO_2} greater than 0.40 (101–104). Consider a 5-kg infant with a minute ventilation of 240 mL/kg/min (1.2 L/min) who is treated with 100% oxygen via nasal cannula at 4 L/min. What is the fraction of room air that this infant can entrain? An average adult with a minute ventilation of 6 L/min has a much greater chance of entraining room air if treated with the same 100% oxygen via nasal cannula at 4 L/min. Nasal interfaces to deliver BiPAP, CPAP, or high-flow nasal cannula (HFNC) may provide enough flow to washout anatomic oropharyngeal dead space as well as prevent entrainment of room air during inspiration. The minute ventilation demands of an individual patient, the flow delivered by the device, as well as the presence of an oral leak may affect the Fd_{O_2} for a given patient. Unfortunately, there are no published studies reporting the effective Fd_{O_2} by nasal modes of NRS. Therefore, in the absence of data to generate a nomogram for estimation of F_{IO_2}, we propose a simple screening algorithm based on normal resting minute ventilation (VE) of an average patient and a predicted F_{IO_2} = 0.40 when the flow is approximately equal to VE (**Table 7**).

Given limitations with practical measurement of Fd_{O_2}, we sought to determine a minimal amount of oxygen therapy that would indicate a patient is at risk for ARDS. Additionally, the infrequent use of arterial catheters in children mandate the use of pulse oximetry in the diagnostic criteria of this at-risk population. Although we wanted to avoid diagnostic criteria that require a maneuver applied at the bedside of patients, the plateau of the oxyhemoglobin dissociation curve when Sa_{O_2} is above 97%, the increased accuracy of SF when Sp_{O_2} is less than or equal to 97%, and the potential for oxygen toxicity with unnecessary delivery of F_{IO_2} require that supplemental oxygen therapy is titrated until Sp_{O_2} less than or equal to 97%. If Sp_{O_2} = 97%, then a patient needs only to be treated with 37% oxygen to have an SF = 264. We propose that patients with oxygen saturations of less than or equal to 97% and treated with nasal modes of NRS using 100% oxygen at flows that are approximately equal to resting minute ventilation be considered at risk for ARDS (**Fig. 2** and **Table 7**). If an oxygen blender is used, the calculation to determine equivalent flow of 100% oxygen = F_{IO_2} × Flow rate (L/min) (e.g., 6 L/min flow at 0.35 F_{IO_2} = 2.1 L/min). Although higher flows used in nasal BiPAP, nasal CPAP, and HFNC may reduce the amount of room air that a patient can entrain during inspiration, these patients will have a higher Fd_{O_2} and therefore a lower SF. In the absence of better data to estimate Fd_{O_2} in a given patient, it is our intent to underestimate Fd_{O_2} and we believe that capturing these patients as "at risk" for ARDS is sufficient. Implementation of these criteria will improve future epidemiologic studies of ARDS in adults and children by facilitating capture of all patients at risk of ARDS. These recommendations are also congruent with the adult National Institutes of Health Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network initiative.

We have elected not to stratify patients receiving NRS into risk severity groups based on hypoxemia criteria due to variability in how noninvasive ventilation is used, paired with the difficulty in estimating delivered F_{IO_2} and mean airway pressure. Therefore, we recommend that children who are on full face mask modes of NRS with a minimum CPAP of 5 cm H_2O who have PF ratios less than or equal to 300 or SF ratios less than or equal to 264 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.

Recommendations:

1.8.1 We recommend that, in order to apply Sp_{O_2} criteria to diagnose PARDS, oxygen therapy should be titrated to achieve an Sp_{O_2} between 88% and 97%. *Strong agreement*

1.8.2 We recommend that defining a group of patients at risk for PARDS is necessary to determine the epidemiology of disease progression and potential avenues for disease prevention. *Strong agreement*

Defining PARDS in Children With Existing Lung or Cardiac Disease

Interpretation of the diagnostic criteria of ARDS in children has varied since the AECC criteria were finalized, and the acceptance and application of the Berlin criteria (2) is unlikely to clarify the issue of exclusion criteria in PARDS. In particular, a number of exclusion criteria have been applied in children by various studies. These have included gestational age, preexisting chronic lung disease, cyanotic congenital heart disease, and coexisting LV failure/dysfunction. However, these preexisting comorbidities do not exclude the potential for these patients to develop PARDS, and these comorbidities represent important at-risk patient populations. Therefore, we believe these must be addressed in a definition of PARDS.

Coexistence of PARDS With Chronic Lung Disease. The Berlin criteria define ARDS occurring within 1 week of a known clinical insult or new/worsening symptoms, providing clarity regarding the occurrence of ARDS on a background of chronic

TABLE 7. Predicted F_{IO_2} in Patients Supported With Nasal Modes of Respiratory Support

Age	Minute Ventilation	Nasal Respiratory Flow	Predicted F_{IO_2}(%)
< 1 yr old	240 mL/kg/min (10-kg infant will breathe 2.4 L/min at rest)	2 L/min 100% O_2	40
1–5 yr old	180 mL/kg/min (25-kg child will breathe 4.5 L/min)	4 L/min 100% O_2	40
5–10 yr old	120 mL/kg/min (45-kg child will breathe 5.4 L/min)	6 L/min 100% O_2	40
> 10 yr old	Adult minute ventilation = 6 L/min	6–8 L/min 100% O_2	40

lung disease. Infants and children with chronic lung disease are at risk of developing PARDS, and many authors have included children with chronic lung disease in ARDS cohorts. Santschi et al (23) found that 36.4% of cases of PARDS involved underlying chronic pulmonary disease and 25.5% of their cohort were also ex-preterm infants. Other authors have found high proportion of children presenting with ARDS with underlying chronic lung disease (Flori et al—11% [8], Erickson et al—10% [5]) and history of prematurity (Flori et al—24% [8]).

In order to develop criteria to define PARDS in children with chronic lung disease, the spectrum of chronic lung disease, ranging from oxygen dependence to various forms of noninvasive ventilation to long-term invasive ventilation, were considered. Since this is a diverse population with some patients with chronic bilateral densities on CXR and others chronically supported with invasive ventilation that at baseline meet hypoxemia criteria for moderate to severe PARDS, it became clear that criteria for degree of change would be arbitrary. Patients that are chronically supported with supplemental oxygen or noninvasive positive pressure mechanical ventilation that require intubation and invasive mechanical ventilation can be stratified into mild to severe PARDS criteria. However, there are no data to support applying severity criteria to patients chronically treated with invasive mechanical ventilatory support. In order to determine whether severity criteria can be applied to these patients, future studies will need to include these patients in the enrollment criteria.

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. Future studies are required to determine whether changes in chest imaging that are consistent with new parenchymal disease will be of diagnostic and prognostic value.

Coexistence of PARDS With Cyanotic Congenital Heart Disease. 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 PARDS 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 the pathologic processes described by Ware and Matthay (105) can occur in children with cyanotic congenital heart disease. Hence, worsening hypoxemia with pulmonary parenchymal disease on CXR in the absence of changes in the underlying cardiac disease may be consistent with a diagnosis of PARDS. Patients with uncorrected cyanotic congenital heart disease may be at high risk of PARDS for a number of reasons: frequent hospitalization, instrumentation, risk of endocarditis, immune compromise, need for palliative procedures and cardiopulmonary bypass, and other associated congenital defects.

Review of the literature is largely unhelpful in defining the association between cyanotic congenital heart disease and ARDS as cyanotic congenital heart disease is listed as an exclusion in most epidemiological studies (5, 8, 11, 18, 23). Of the patients screened by Santschi et al (23) who fulfilled ARDS criteria (a known acute cause of ARDS, significant hypoxemia and bilateral CXR changes), 73 of 414 (17.6%) were excluded due to presence of cyanotic congenital heart disease.

Hu et al (27), in a large cohort study in China, included patients with congenital heart disease (8.5%) but did not specify whether any patients had uncorrected cyanotic congenital heart disease. On review of both the AECC and Berlin criteria, uncorrected cyanotic congenital heart disease is not listed as an exclusion criterion, although it has been applied as an exclusion criterion by many investigators.

Children with chronic cardiac disease, both cyanotic congenital cardiac disease and noncyanotic disease, are likely to be an important group of patients with high morbidity and mortality from PARDS. The diagnosis of PARDS in these children will require individual providers to exclude new changes in intracardiac shunt/mixing or worsening LV dysfunction as the cause of worsening hypoxemia. Children with a known acute clinical insult, chest imaging consistent with parenchymal lung disease, and an acute deterioration in oxygenation not explained by changes in underlying cardiac disease should be considered to have PARDS.

Echocardiography is not ideal for assessment of changes in intracardiac shunt or mixing. However, echocardiography 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, and increasing pulmonary hypertension). More invasive modalities, such as cardiac catheterization, CT angiography, and MRI, while useful in defining intracardiac shunts, pose significant risks in children with PARDS.

Given the difficulties in ascribing the contribution to hypoxemia from acute lung disease versus intracardiac shunt, future studies will need to include patients with cyanotic congenital heart disease to determine whether PARDS severity criteria can be applied to these patients.

Recommendations:

1.9.1 We recommend 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. *Strong agreement*

1.9.2 We recommend that 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. *Strong agreement*

1.9.3 We recommend that children with chronic lung disease who are on invasive mechanical ventilation at baseline or cyanotic congenital heart disease with acute onset of illness that satisfy PARDS criteria should not be stratified by OI or OSI risk categories. Future studies are necessary to determine

PARDS risk stratification of patients with acute on chronic hypoxemic respiratory failure. *Strong agreement*

1.9.4. We recommend that future studies of PARDS should endeavor to include children with preexisting pulmonary and cardiac disease. *Strong agreement*

This has allowed us to arrive at the preceding draft definition of PARDS (**Figs. 1** and 2).

DISCUSSION

We have attempted to create a pediatric-specific definition for ARDS that builds on the adult-based Berlin definition, but has been modified to account for the unique epidemiology, practice patterns, comorbidities, and differences in outcome between adults and children with ARDS. The definition is largely based on consensus opinion, supported by existing literature when available, and specific aspects of the definition have been tested with available empirical data.

Several aspects of the PARDS definition are identical to the Berlin Definition of ARDS: namely, timing of ARDS after a known risk factor and the potential for ARDS to coexist with LV dysfunction. We elected to stay consistent with the Berlin definition for these elements because pediatric literature and practice patterns support similarities with adult literature and practice. In addition, although there are age-related differences in lung morphogenesis that may modify incidence, outcome, and severity of ARDS in children compared with adults, there are insufficient data to support any specific age for "adult" or "pediatric" ARDS. On the other end of the age spectrum, there are clear differences in the pathobiology of PARDS and hypoxemic respiratory failure that occur in the perinatal period, justifying specific exclusion of these patients from the definition of PARDS. Larger departures from the Berlin Definition surround 1) the elimination of the requirement of bilateral infiltrates on chest imaging; 2) the use of OI and OSI instead of PF ratio with a minimum PEEP level (51); 3) the specific inclusion of children with preexisting chronic lung disease or cyanotic congenital heart disease; and 4) the creation of "at-risk" criteria to facilitate future epidemiologic studies of PARDS, and assist with earlier identification of patients, as consistent with the adult NIH PETAL initiative.

The goal of a pediatric-specific definition for ARDS is to provide the basis for consistent identification of a heterogeneous syndrome with a variety of causes. The definition may facilitate future epidemiological research as well as evaluation of specific therapies and prevention strategies. On a population level, our hope is that stratification of severity groups will allow robust evaluation of the risks and benefits of potential therapies. However, caution must be used when applying this definition to individual patients given the multitude of pulmonary and extrapulmonary factors that contribute to outcome for children with PARDS.

LIMITATIONS

There are certainly limitations with our definition. First, there were insufficient data to test several of the recommendations. We hope future research will target some of these aspects of the definition, and we advocate iterative improvements and revision of the definition as more data become available. Second, much of the data available for analysis were generated as part of clinical investigations conducted by members of the PALICC group. Given that most of these data were from larger academic PICUs, it is possible that the cut points used for the risk groups are not as generalizable to the global management of PARDS. This should be tested with external data. Third, we have included OSI in the definition of PARDS when OI is not available. Although there has been a recent retrospective study examining the relationship between OSI and mortality (90), studies validating the use of OSI in PARDS are sparse and there are not sufficient data to examine whether the risk severity groups generated from OSI result in similar mortality rates as those generated with OI. This should be tested in a future study.

CONCLUSIONS

In conclusion, we have developed a pediatric-specific definition of ARDS based largely on consensus opinion from established investigators in PARDS, with some validation using data from existing PARDS studies. We propose using this definition for future investigations and clinical care of children with PARDS and encourage external validation with the hope for continued iterative refinement of the definition.

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APPENDIX 1: Pediatric Acute Lung Injury Consensus Conference Group

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

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

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

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

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

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

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

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

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

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

Literature Search Methodology: Melania Bembea, Johns Hopkins University