Pediatric Acute Respiratory Distress Syndrome

A Clinical Guide

Steven L. Shein
Alexandre T. Rotta
Editors

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To my parents, Jeff and Diane, and brother, David, thank you for all of your support growing up. To my countless teachers, mentors, co-residents, co-fellows, and all the rest at CWRU, RBC, and CHP, thanks for teaching me and being in the trenches with me. To my wife, Monica, and my children, Jack and Emily, thank you for your love, your support, your patience, your understanding, your hugs, and your laughter. And to all of the parents and families who have permitted me to care for their critically ill loved one, thank you for the privilege of doing so.

Steven L. Shein

To my parents, Enio and Newra, for their contagious love for medicine. To my brother, Francisco, for setting the bar so high. To my mentor, Ashok, for showing me the way. To my teachers, Brad and David, for all the knowledge. To my wife, Kristy, and my daughters, Ashlynn and Valentina, for their encouragement, support, sacrifices, patience, and unconditional love.

Alexandre T. Rotta

Preface

In 1967, Ashbaugh and colleagues described a group of predominantly adult patients with various underlying conditions who developed a peculiar form of respiratory failure. Regardless of the inciting etiology, these patients shared a common rapid progression to respiratory failure with hypoxemia, diffuse infiltrates on chest radiographs, decreased lung compliance, and decreased functional residual capacity, requiring the application of positive end-expiratory pressure (PEEP) to improve oxygenation. This condition, which we now know as the acute respiratory distress syndrome (ARDS), was based on somewhat vague diagnostic criteria and was not specific enough to exclude other medical conditions with similar manifestations.

Our understanding of ARDS has increased greatly during the past five decades. ARDS definitions and diagnostic criteria have also evolved over time, including the Murray Lung Injury Score (1988), the American-European Consensus Conference Definition (1994), and the Berlin Definition (2012) put forth jointly by the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM). Each of these definitions represented a step forward in delineating this important diagnosis, yet the applicability of these adult-centric definitions had significant limitations for children since they did not consider ARDS factors germane to the pediatric patient.

The lack of a pediatric-specific ARDS definition, coupled with a rapidly growing body of literature on children with acute hypoxemic respiratory failure, led an expert panel to assemble the Pediatric Acute Lung Injury Consensus Conference (PALICC, 2015) and put forth the first definition of pediatric ARDS (PARDS). This definition represented a major step forward for those involved in PARDS diagnosis, treatment, and research. It provided the framework that would allow for comparisons across multiple institutions, helped define the actual worldwide prevalence of this condition, and clarified the role of various treatment modalities and their impact on outcomes.

This textbook will provide a comprehensive review of the available and emerging science related to PARDS, discuss state-of-the-art treatment modalities and strategies, and reflect on clinical outcomes for this important condition. The various chapters were written by established experts in the field of PARDS, many of whom participated in the original PALICC effort.

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We are grateful for the diligent work and dedication of our contributors, without whom this book would have never amounted to more than an idea. We are also thankful to Sheik Mohideen, Andy Kwan, and the entire team at Springer Nature for keeping us on track and for their expert assistance.

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The History of ARDS and the Need for a Pediatric Definition

1

Howard Eigen

The history of acute respiratory distress syndrome (ARDS) is long, complex, and very interesting. It is one of the few conditions first named in children, in this case neonates with infant respiratory distress syndrome (IRDS), also known as hyaline membrane disease. The term was then applied to adults with acute respiratory failure exhibiting clinical and pathophysiological features closely resembling those of the neonatal counterpart. It is likely that the clinical entity we now know as ARDS has existed for centuries, yet its recognition as an organized syndrome did not occur until just over half a century ago.

The initial description of pulmonary hyaline membranes is generally attributed to Hochheim [1], who, in 1903, described 2 neonatal cases at autopsy and attributed the presence of alveolar membranes to the aspiration of amniotic sac contents. They were first described in the English-language literature in 1925 by Johnson [2], who regarded hyaline membranes as a form of neonatal pneumonia. The studies of Farber in the 1930s attributed pulmonary hyaline membranes to the peripheralization by respiratory activity of aspirated amniotic sac contents – particularly vernix – into the distal airways of the lung [3, 4]. This concept of IRDS remained predominant until the mid-1950s.

In 1959, James [5] contributed new observations of the clinical features of IRDS because of the then novel practice of caring for these infants, unclothed in clear-walled incubators, which allowed for the observation of the patient struggling through several hours of rapid and labored breathing with deep sternal and intercostal retractions alternating with periods of apnea. This is similar to how the understanding of ARDS evolved: the rudiments of the pathology and the clinical course were each identified separately, without a full understanding of the links between them.

Perhaps the earliest published description of ARDS came in 1821 when Laennec characterized anasarca of the lungs and pulmonary edema without heart failure in his book "Treatise on Diseases of the Chest." The concept of ARDS as an unnamed clinical entity certainly was known early in World War I. A military medical textbook published in 1915 and used by Canadian armed forces during World War I contains a graphic description of ARDS in relation to a poison gas attack: "Edema of the lungs, with general asphyxia. Livid cyanosis with great dyspnea is the outstanding clinical feature. A yellow serous fluid fills the air passages in such quantities that it may drip from the mouth of the living patient when the stretcher is tilted head downwards. Death in this stage may occur at any time from the first to the fourth or fifth day." [6] Concomitantly, physicians

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in World War I established the relationship between trauma and a sudden and severe respiratory failure ultimately leading to death, then termed "posttraumatic pulmonary massive collapse." [7]

A 1946 publication by Brewer and colleagues [8] described the "wet lung" in the following manner: "In handling this large number of casualties it was found in the forward hospitals in particular, that those cases with dry lungs gave us very little trouble. On the other hand, those showing a wet pulmonary tree were difficult to resuscitate from shock." By the close of World War II, the syndrome of "wet lung" had been characterized further, in which life-threatening respiratory distress complicated the progressive recovery from hemorrhagic and traumatic shock incurred during combat.

During the Vietnam War, as the survival rate following circulatory collapse on the battlefield improved, the syndrome was frequently identified, but under various names. Thus, "wet lung," "shock lung," "transfusion lung," or "Da Nang lung" became synonyms for severe acute respiratory failure that followed successful resuscitation from circulatory collapse. The sequence was similar in all of those named syndromes: severe nonthoracic injury, blood loss, and hypotension acquired during combat, successful resuscitation on the battlefield, and prompt evacuation to a medical facility for further management. In a few days, there followed progressive respiratory distress and failure. Although only a small fraction of those who reached the hospital developed "shock lung," in those who did, the pattern of evolution was consistent: insidious onset of rapid shallow breathing, crackles, refractory cyanosis, radiographic appearance of enlarging interstitial and alveolar infiltrates with the entire lung eventually enveloped in a diffuse haze, and a chest radiographic "white out." Administration of high oxygen concentrations and assisted ventilation became less and less effective, followed by death resulting from respiratory insufficiency often complicated by circulatory collapse.

In 1967, Ashbaugh and colleagues [9] published a more detailed, systematic, and cohesive description of the syndrome based on the clinical course of 12 patients with acute respiratory failure that did not respond to usual methods of respiratory support. These patients had tachypnea, hypoxemia, and loss of lung compliance following a variety of insults, exhibiting clinical and pathological characteristics thought to be "remarkably similar to the infantile respiratory distress syndrome" [9]. In a follow-up publication in 1971, Petty and Ashbaugh [10] used the term *adult* respiratory distress syndrome, presumably not to exclude children from the diagnosis, but in an attempt to distinguish it from the well-established IRDS. In fact, one of the patients described in the original cohort was an 11-year-old with the ARDS clinical syndrome, and 4 others were teenagers (18- and 19-year-olds) that would have been routinely cared for by pediatric intensivists in the current era.

The incidence and recognition of the adult respiratory distress syndrome increased dramatically after 1967, coinciding with the height of the Vietnam War. With the advent of better treatments in the field and rapid staged evacuations, more casualties survived to reach higher-level care and had time to develop ARDS, or before 1967, one of its synonyms (Box 1.1). Given the magnitude of the disease in morbidity, mortality, and cost, a clear, widely accepted, and clinically useful ARDS definition was needed.

Over the next couple of decades, ARDS continued to be an important cause of morbidity and death. Nevertheless, the heterogeneous nature of

Box 1.1 ARDS Historical Synonyms

- Congestive atelectasis
- Wet lung
- Hemorrhage lung
- Shock lung
- Pump lung
- Trauma lung
- Transfusion lung
- White lung
- Da Nang lung
- Adult hyaline membrane disease
- Adult respiratory distress syndrome

Table 1.1 The American-European Consensus Conference definition of ARDS

	Timing	Oxygenation	Chest radiograph	Pulmonary artery wedge pressure
ALI criteria	Acute onset	$PaO_2 \leq 300$ mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤18 mm Hg when measured or no evidence of left atrial hypertension
ARDS criteria	Acute onset	$PaO_2 \leq 300$ mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤18 mm Hg when measured or no evidence of left atrial hypertension

PEEP positive end-expiratory pressure, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome

ARDS created great difficulty in determining its true incidence and outcomes, especially in the absence of a clear definition. As an example, the published ARDS mortality rate varied between 10% and 90%, and its reported incidence differed vastly between European countries and the United States [11]. This was due to, at least in part, the lack of an agreed upon definition among various countries, or even among different studies within the same country. In an attempt to bring clarity and uniformity to the definition of ARDS, a series of meetings were held under the auspices of the American Thoracic Society and the European Society of Intensive Care Medicine in 1992. The American-European Consensus Conference on ARDS (the AECC) was convened with the charge of not only defining ARDS, but also to bring light to the issue of incidence, focus on the emerging understanding of pathophysiologic mechanisms, and establish guidelines for the conduct and coordination of clinical studies. The AECC published its position paper in 1995, but the formal definition was not easily arrived at, as some participants suggested that the definition of ARDS should be different for research, epidemiology, and individual patient care. Early on, it was decided that there should be a return to the term "acute" (rather than "adult") respiratory distress syndrome in recognition of the fact that ARDS is not limited to adults. Unfortunately, the AECC also introduced the term acute lung injury (ALI) to the definition, in an effort to characterize the less severe end of the ARDS spectrum. Later on, this simply caused confusion as the cutoff points for ARDS and ALI became a topic for debate. More recently, ALI has been dropped from general usage and termed "mild ARDS."

The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen ratio [PaO_2/FIO_2] ≤200 mm Hg) with bilateral infiltrates on a frontal chest radiograph, with no evidence of left atrial hypertension (Table 1.1). The AECC did not consider the type or intensity of respiratory support to be a requirement in defining ALI or ARDS because resources for ventilator therapy and physician practice patterns vary considerably. Also, there are many cases in which mechanical ventilation is intentionally withheld because of patient request or a determination that aggressive support is futile. In general, it is best to keep disease definitions independent of the therapy used to treat them. Definitions of any disease states suffer at the margins, usually at the lower end of the severity spectrum.

Nearly 2 decades later, the Berlin Conference was organized to clear up multiple issues regarding the reliability and validity of the AECC definition. The ARDS conceptual model proposed by the Berlin Conference stated that ARDS is a type of acute diffuse, inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities. These are associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (i.e., edema, inflammation, hyaline membrane, or hemorrhage). The Berlin Conference proposed three disease severity categories and tested outcomes of these categories against a validation dataset of previous cases (Table 1.2). Using the Berlin definition, patients

Table 1.2 The Berlin definition of ARDS

Acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema in no risk factor present
Oxygenation[b] Mild Moderate Severe	200 mm hg < PaO_2/FiO_2 ≤ 300 mm hg with PEEP or CPAP ≥5 cm H_2O[c] 100 mm hg < PaO_2/FiO_2 ≤ 200 mm hg with PEEP or CPAP ≥5 cm H_2O PaO_2/FiO_2 ≤ 100 mm hg with PEEP or CPAP ≥5 cm H_2O

CPAP continuous positive airway pressure, *FiO_2* fraction of inspired oxygen, *PaO_2* partial pressure of arterial oxygen, *PEEP* positive end-expiratory pressure
[a]Chest radiograph or computed tomography scan
[b]If altitude higher than 1000 m, the correction factor should be calculated as [PaO_2/FiO_2 × (barometric pressure/760)]
[c]This may be delivered noninvasively in the mild ARDS group

with mild, moderate, or severe ARDS exhibited incremental mortality (27%, 32%, and 45%, respectively), as well as increased median duration of mechanical ventilation in survivors [12]. Compared with the AECC definition, the final Berlin definition had better predictive validity for mortality and was rapidly accepted worldwide for its overall superiority.

Both the AECC and Berlin definitions of ARDS were created without specific consideration to ARDS that occurs in children. If a case were to be made for a separate pediatric definition, it must have been made on the basis that the current definition for adults does not properly characterize the disease in children. Unlike in adults with ARDS, the Berlin definition severity stratification fails to show an incremental mortality between children with mild and moderate ARDS at 6, 12, or 24 hours from diagnosis [13]. Any new template proposed for PARDS should be carefully drawn so as to properly characterize the syndrome and show what elements are unique to the disease in children.

In 2015, Pediatric Acute Lung Injury Consensus Conference (PALICC) published the much needed and long overdue first pediatric-specific definition of ARDS [14]. In addition, it put forth consensus recommendations regarding therapies for pediatric acute respiratory distress syndrome (PARDS), defined a subset of patients considered to be "at risk" for PARDS, addressed PARDS in specific populations (i.e., cyanotic heart disease, chronic lung disease, left ventricular dysfunction), and delineated priorities for future research. The definitions and recommendations were developed over the span of 2 years by 27 experts in the field of PARDS representing 21 academic institutions from 8 countries in 3 continents. The PALICC experts evaluated clinical issues on 9 topics related to PARDS and developed and voted on 151 recommendations. Strong agreement (meaning that all experts rated the recommendation 7 or higher on a scale of 1–9) was reached in 132 recommendations.

The PARDS definition was a central component of the PALICC report [14]. Like the Berlin definition, PALICC determined that the onset of PARDS must occur within 7 days of a known clinical insult and the respiratory failure must not be fully explained by cardiac failure or fluid overload. Significant changes from the Berlin definition included abandoning the PaO_2/FiO_2 ratio in the grading of PARDS severity (mild, moderate, and severe) in favor of the oxygenation index (OI) or the oxygen saturation index (OSI). Using the OI or the OSI allows for a more precise appreciation of the role of mechanical ventilation support on oxygenation and severity of illness classification. The presence of bilateral pulmonary infiltrates is no longer a requirement in the PALICC definition, since there is no evidence that pediatric patients with unilateral pulmonary involvement have different clinical courses and outcomes than those with bilateral disease. PALICC deliberately chose not to specify age criteria for PARDS, but it should be understood that the definition is intended to cover the demographics generally cared for by pediatric intensivists and excludes neonates with perinatal-

related lung disease (e.g., meconium aspiration, hyaline membrane disease, alveolar capillary dysplasia). Chapter 2 covers the PALICC definition in detail.

ARDS has had a longer history than many would think. Our understanding of this important syndrome was built through thoughtful and astute clinical observations with the ultimate goal of making therapy more effective and improving patients' lives. It is clear that the disease in children is distinct from that in adults, so although ARDS definitions have evolved over time, the recent development of a pediatric-specific definition has been widely welcomed by the critical care community. This much needed thoughtful and relevant new PARDS definition provides a unifying language for those caring for critically ill children or advancing the field through research.

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2 Pediatric Acute Respiratory Distress Syndrome: Definition and Epidemiology

Fernando Beltramo and Robinder G. Khemani

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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S. L. Shein, A. T. Rotta (eds.), *Pediatric Acute Respiratory Distress Syndrome*,
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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
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</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
5 ≤ OSI < 7.5[a]</td><td>8 ≤ OI < 16
7.5 ≤ OSI < 12.3[a]</td><td>OI ≥ 16
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
Chronic lung disease: Standard criteria with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline
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
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</td><td>Oxygenation</td></tr>
<tr><td>Nasal mask CPAP or BiPAP
FiO_2 ≥ 40% to attain SpO_2 88–97%</td></tr>
<tr><td>Oxygen via mask, nasal cannula, or high flow
SpO_2 88–97% with oxygen supplementation at minimum flow[b]:
<1 year: 2 L/min
1–5 years: 4 L/min
5–10 years: 6 L/min
>10 years: 8 L/min</td></tr>
<tr><td>Invasive mechanical ventilation
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-