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**Review article in:**

# Last updates on the management of pediatric acute respiratory distress syndrome

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**Definition:**

Is a clinical syndrome caused by disruption of the alveolar epithelial–endothelial permeability barrier unrelated to cardiogenic pulmonary edema. Injury may occur directly to the alveolar epithelium (ie, pneumonia, inhaled toxins, etc.) or indirectly to the capillary endothelium secondary to systemic inflammation as seen in conditions such as sepsis or pancreatitis [1].

**Pathophysiology:**

ARDS follows cascade of events after direct pulmonary or systemic insult resulting into the disruption of alveolar-capillary unit. The pathophysiology of ARDS is complex and multifaceted involving 3 distinct components: (1) nature of the stimulus (2) host response to the stimulus, and (3) the role of iatrogenic factors. To understand this complex process, it is important to understand the physiology and functional anatomy [2].

Disruption of the alveolar endothelial barrier leads to accumulation of protein-rich fluid in the alveoli. Dysregulated inflammation and coagulation then ensue, resulting in impaired lymphatic drainage and surfactant degradation. Resolution of the inflammation usually occurs after several weeks, with potential development of fibrosis [3].

**Etiology**:

The most common cause of ARDS in children is viral respiratory infection, although ARDS can be associated with many other underlying conditions, including pneumonia, sepsis, trauma, burns, pancreatitis, and cardiopulmonary bypass [3].
Ventilator induced lung injury (VILI) has also been documented as one of the etiologies [4].

**Epidemiology and Mortality:**

Respiratory failure is the most common cause of death for children admitted to pediatric intensive care units (PICUs), and ARDS accounts for 1%–10% of PICU admissions. Mortality

rates in PARDS are highly variable across studies, likely attributable to varying comorbid conditions and different etiologies. A meta-analysis found the pooled mortality rate in PARDS to be approximately 24%, with an overall downtrend in mortality over the last 3 decades.

Cause of death in PARDS is variable, given the heterogenous etiology of the disease process. In a large retrospective study, neurologicfailure andmultisystem organ failurewere the primary causes of early and late deaths, respectively, and only a minority of deaths were attributed to refractory hypoxemia. Significant predictors of mortality include immunocompromised state, multiorgan dysfunction, older age, and severity of hypoxemia. infectious PARDS was associated with lower severity of illness andmortality compared with noninfectious PARDS. Moreover, immunocompromised state, a well-described predictor of mortality in ARDS, was not found to be associated with mortality in noninfectious PARDS. Overall, PARDS mortality has decreased in the last few decades and is lower than adult ARDS mortality, which ranges from 35% to 46% with mild to severe. However, PARDS mortality remains significant, and improvements in identification, risk stratification, and targeted management will be crucial to further reduce the mortality burden [5,6.].

**Clinical presentation:**

The key presenting symptoms are respiratory distress (inability to breathe normally) or strained breathing that increases fatigue (fatigued breathing). Patients will normally present themselves with labored breathing, tachypnea, and intercostal retractions, as well as suprasternal retractions. “Crackles” noted on lung auscultation are usually involved with this presentation, and rales, rhonchi, or wheezes may also appear. Dyspnea usually occurs first, along with rapid, shallow respiration. The patient’s skin may appear cyanotic or mottled. The onset of PARDS occurs within 1 week from known or suspected clinical insult [7].

**Ddx**:

1. septic shock
2. Bacterial Pneumonia
3. Airway Foreign Body Imaging
4. Aspiration Pneumonitis and Pneumonia
5. congestive heart failure

6. Hypersensitivity Pneumonitis

7. Acute Poststreptococcal Glomerulonephritis

8. cardioginc pulmonary edema

9. diffuse alvealar hemorrhage

10. pneumothorax

11. Fat embolism

12. Constrictive Pericarditis

13. Goodpasture Syndrome

14. Gastroesophageal Reflux Disease (GERD) Imaging [12]

**Investigations:**

**1. Chest imaging including:**

A. a radiograph and/or a computed tomogram: chest x-ray findings are indistinguishable from those of cardiogenic pulmonary edema, Bilateral infiltrates may be patchy or asymmetric and may include pleural effusions (fig. 1). Computed tomographic scanning has demonstrated that alveolar filling, consolidation, and atelectasis occur predominantly in dependent lung zones, whereas other areas may be relatively spared (fig. 1) [8].

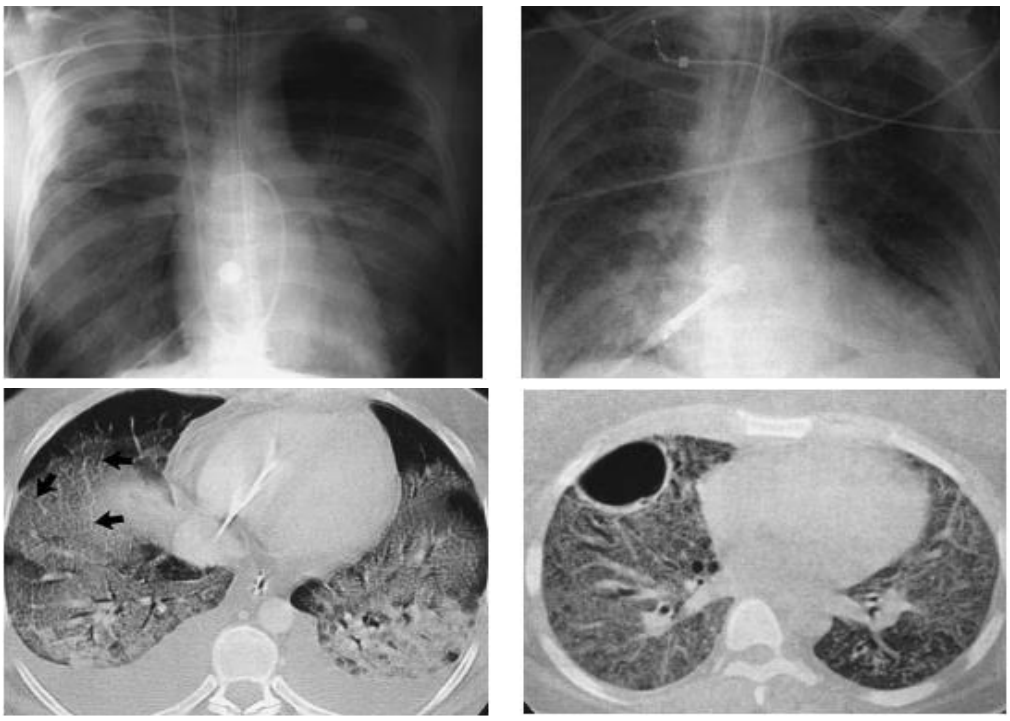

Figure 1. Radiographic and Computed Tomographic (CT) Findings in the Acute, or Exudative Phase and the Fibrosing-Alveolitis Phase (Panels B and D) of Acute Lung Injury and the Acute Respiratory Distress Syndrome.

**B. altrasonography:** is an easy method of further assessing pleural effusions and differentiating between transudative and exudative fluid (The only role for chest ultrasonography in patients with ARDS is to define the presence of pleural effusions and to determine whether loculation of the pleural fluid is present if drainage of the effusion is being considered. [8]

**C. echocardiography:** The primary role of echocardiography in ARDS is to detect congenital or acquired heart disease as a cause of respiratory distress and pulmonary edema. Echocardiography may provide evidence of pulmonary hypertension; however, the practical implications of this finding are unclear, because little evidence supports the clinical benefit of pulmonary vasodilators in ARDS. [8]

D. **MRI:** no data are available concerning the role of MRI in patients with ARDS. [8]

**2. Hematological tests:**

**A.arterial blood gas (ABG) measurements:** The onset of capillary congestion and changes in the alveolar epithelium during the initial exudative stage leads to significant ventilation/perfusion (V/Q) mismatching and intrapulmonary shunting. During this stage of ARDS, oxygen diffusion is impeded to a much greater extent than carbon dioxide diffusion. Respiratory alkalosis reflecting a relative hyperventilation and hypocarbia is an early sign of ALI/ARDS. This difference is attributable to the much greater solubility of carbon dioxide. [8]

**B. complete blood count (CBC) with differential:** The CBC may indicate an infectious etiology. Leukocytosis may be evident, reflecting either the initiating stimulus or a nonspecific inflammatory response. The CBC may also uncover significant anemia, which will further compromise oxygen-carrying capacity. Anemia may secondary to acute illness, underlying chronic disease, acute blood loss, or hemodilution from massive fluid resuscitation. Thrombocytopenia may be present. [8]

**C. an electrolyte panel with blood urea nitrogen (BUN) and creatinine:** An electrolyte panel may also screen intravascular volume status, anion gap acidosis, and other potential comorbidities. Additional laboratory tests would be indicated pending specific concerns toward individual patients. [8]

**Management:**

Recognizing that ARDS in children is different than adults, an international panel of experts convened the Pediatric Acute Lung Injury Consensus Conference (PALICC) to establish new definitions and guidelines for pediatric acute respiratory Distress syndrome (PARDS).

The 2015 PALICC definition broadens the radiographic requirement to include any new parenchymal infiltrate(s). Additional key differences in the PARDS definition include allowing use of pulse oximetry to avoid underestimating ARDS prevalence in children if arterial blood oxygenation measurements are not available and SpO2 £ 97%, and utilization of the oxygenation index (OI) [(FiO2 · mean airway pressure · 100)/PaO2] and oxygenation saturation index (OSI) [(FiO2 · mean airway pressure · 100)/ SpO2] rather than the PaO2/FiO2 (P/F) ratio to assess hypoxemia [9].

**PARDS baseline criteria based on PALLIC guidelines**:

1. Acute onset; within 7 days of clinical insult

2. Chest imaging (radiograph or computed tomography) findings of new infiltrates (unilateral or bilateral) consistent with

acute parenchymal disease.

3. Edema not fully explained by fluid overload or cardiac failure

May present as new acute lung disease in setting of chronic lung disease and/or heart disease

4. Exclusions of Perinatal lung disease. [9]

**PARDS severity stratification**:

The PALICC criteria were recently compared to historical and subsequent definitions (Berlin, AECC) in 2 studies of pediatric patients in the intensive care unit (ICU). Both studies concluded that the new criteria identified a higher number of PARDS patients; patients meeting PALICC criteria for PARDS were found to have a lower overall mortality rate and a lower proportion of severe ARDS and complications. Even more recently, the prospective international Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study, the largest PARDS study using the PALICC definition, demonstrated in over 700 children that the PALICC definition identified more children as having PARDS than the Berlin definition. [9]

## Treatment:

Goals of PARDS managment are:
1. treat the underlying cause 2. provide adequate oxygenation and ventilation 3. protect the lungs from ventilator-induced lung injury (VILI)

## Standards of Care:

**A. Lung-protective ventilation:**

The aims of lung-protective ventilation are to avoid overdistension (volutrauma and barotrauma), minimize the cyclic opening and closing of alveoli (atelectrauma), and minimize injurious effects of biochemical mediators on the lung and distal organs (biotrauma)

The PALICC guidelines recommend tidal volumes of 3–6 and 5–8mL/kg for patients with poor and more preserved respiratory compliance, respectively, along with limiting inspiratory plateau pressure to 28 cm H2O.

To minimize the potential toxicity of ventilatory support required to oxygenate and ventilate PARDS patients, permissive hypoxemia and hypercapnia should be considered. PALICC recommends oxygen saturation goals of 92%–97% for mild PARDS and 88%–92% and PEEP >10 cm H2O for severe PARDS. [9]

**B. fluid management:**

To date, no pediatric RCTs have investigated fluid management strategies in PARDS. Two opposing strategies exist:

(1) fluid resuscitation to maintain adequate cardiac output and extrapulmonary organ function in the setting of widespread inflammation (2) fluid restriction to minimize pulmonary edema.

Several observational studies have evaluated fluid management in pediatric ARDS. In 2011, an observational study suggested that positive fluid balance was associated with increased mortality and prolonged mechanical ventilation, independent of multisystem organ failure and

severity of hypoxemia [10]. PALICC recommends a goal-directed fluid management protocol

maintain intravascular volume while minimizing fluid overload. PALICC recommendations reflect the need to balance end-organ function with the development of pulmonary edema

**C. Sedation**

Adequate sedation of the mechanically ventilated child will ideally optimize patient safety and respiratory support while providing analgesia and anxiolysis to maintain the child in a calm but responsive state. PALICC recommendations supporting targeted sedation to ensure that patients can tolerate mechanical ventilation to optimize oxygen delivery, oxygen consumption, and work of breathing. [11]

## Adjunctive therapies:

**A. High-frequency ventilation:**

When CMV fails, high-frequency oscillatory ventilation (HFOV) is often used as a ‘‘rescue’’ strategy for refractory hypoxemia. Two recent adult RCTs, suggest No benefit, potential harm in adult ARDS (RCTs). However, Small pediatric Randomized controlled trials and observational studies show improved oxygenation but no difference in mortality, duration of MV, or LOS. [12,13]

PALLIS recommandation, Consider HFOV in patients with moderate to severe PARDS and plateau >28 cm H2O

**B. Prone positioning:**

Its efficacy and safety in ARDS have been studied extensively over the last 2 decades, primarily in adults. systematic review of 20 clinical studies representing 297 adult and pediatric patients found improved oxygenation after prone positioning with rare adverse events [14]. Recent meta-analyses studies have assessed the impact of prone positioning on mortality in adults with ARDS, with varying results. The most recent meta-analysis in 2014 of 11 RCTs found a significant reduction in ARDS mortality with prone positioning when coupled with lung protective ventilation, reported a 50% mortality reduction with prone positioning in adults with severe ARDS [15].

The PALICC guidelines recommend considering prone positioning as an option in cases of severe PARDS, but cannot recommend its use as a routine therapy in PARDS given the current pediatric data.

**C. Neuromuscular blockade:**

Neuromuscular blockade (NMB) is an important adjunct to sedation for mechanically ventilated patients to achieve optimal oxygen delivery and lung mechanics. To date, no RCTs have evaluated the utility of NMB in children with PARDS

PALICC recommends considering NMB in children with PARDS if sedation alone is inadequate to achieve effective mechanical ventilation, targeting the minimal effective dose.

**D. Nitric oxide:**

Nitric oxide (NO) is produced in the vascular endothelium and causes relaxation of smooth muscle. Inhaled NO (iNO) has been used as a pulmonary vasodilator to increase blood flow to areas with adequate ventilation, thus improving ventilation/perfusion mismatch and oxygenation in diseases such as ARDS. A meta-analysis of 14 RCTs studying the effect of iNO in >1,300 adults and children with Acute lung injury and ARDS found transient improvement in oxygenation but no reduction in mortality Given iNO has not been shown to improve patient outcomes in PARDS. [16]

PALICC does not recommend its routine use However, the guidelines suggest considering iNO in patients with known pulmonary hypertension, severe right ventricular dysfunction, or as a bridge to extracorporeal life support in severe cases.

**D. Surfactant:** Surfactant dysfunction is part of the known pathophysiology of ARDS, and surfactant replacement has had great success in infantile respiratory distress syndrome. However, pediatric clinical trials of surfactant replacement have not demonstrated a clear improvement in outcomes outside of the neonatal population PALICC guidelines do not recommend routine use of surfactant in PARDS, but recommend further studies to determine if other specific populations may benefit.

**E. Steroids:**

A 2018 meta-analysis evaluating 9 RCTs of low-to-moderate dose prolonged glucocorticoid treatment in adult ARDS reported moderate-to-high evidence that steroid therapy is safe and reduces duration of mechanical ventilation, ICU and overall Length of hospital stay, and mortality. [17] A small pediatric RCT investigating the use of methylprednisolone in PARDS found no difference in mortality, duration of mechanical ventilation, ICU, or Length of hospital stay with steroid therapy. [18] A larger observational PARDS study found fewer ventilator-free days

and longer duration of mechanical ventilation with corticosteroid exposure >24 h.[19] Given the lack of clear evidence in pediatrics, PALICC recommends against corticosteroids as routine therapy in PARDS pending further Studies in specific populations.

**F. Extracorporeal membrane oxygenation:**

Successes with extracorporeal membrane oxygenation (ECMO) in severe neonatal respiratory failure have led to its use in children and adults. In PARDS, ECMO can augment systemic oxygen delivery to allow the injured lungs to rest and recover. However, ECMO carries significant risk and requires substantial resources and expertise.

The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial in adults found that ECMO was cost-effective and increased 6-month disability-free survival. However, the recent ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial showed no significant difference in 60-day mortality in adults with severe ARDS supported with ECMO when compared to CMV. [19]
Unfortunately, despite strong evidence in neonates81–85 and potential benefit in adults,[20] clinical trial evidence for ECMO use in PARDS is lacking. Despite this lack of definitive data, ECMO use in children increased substantially from 2009 to 2015, with a 50% increase in the

number of centers reporting pediatric ECMO cases and a 24% annual increase in pediatric ECMO cases over that time period. [21]

PALICC guidelines suggest that ECMO should be considered in severe PARDS when toxic support is needed to maintain gas exchange. However, ECMO should only be considered after serial evaluations demonstrate deteriorating trends and if the disease process is deemed reversible or if lung transplant is a suitable treatment.

**Conclusion:**

PARDS remains a disease process with significant morbidity and mortality. However, with improved understanding of its epidemiology and heterogeneity in the last decade, as well as ever-growing gains in risk stratification, the future
is ripe with opportunity for more tailored clinical trials to determine best treatment strategies and improve outcomes.

Despite the importance of PARDS as a substantial source of pediatric morbidity and mortality, high-quality data around potential treatments are lacking, which limits our understanding of which therapies lead to optimal outcomes in our PARDS patients. Not surprisingly, this paucity of definitive evidence has led to significant PARDS management variability across centers. A 2013 survey of 59 centers across 12 countries demonstrated that adjunctive therapies are commonly utilized in clinical scenarios consistent with PARDS.90 More than 80% of respondents reported that they would use iNO, three-quarters would prone patients, and around half would consider exogenous surfactant, despite a lack of evidence to support the efficacy of these adjuncts.

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