

# Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) Study

---

**Protocol Version 1.01**

**Version Date: October 3, 2016**

## **Pediatric ARDS Incidence and Epidemiology (PARDIE)**

### **Synopsis**

The Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study represents an international initiative with representation from the Pediatric Acute Lung Injury and Sepsis Network Investigators (PALISI), the European Society of Pediatric and Neonatal Intensive Care (ESPNIC), the Australia and New Zealand Intensive Care Society (ANZICS) and numerous individual international intensive care units. The main goal of PARDIE is to better understand the implications of the new Pediatric Acute Lung Injury Consensus Conference (PALICC) definition of Pediatric ARDS on the incidence and epidemiology of pediatric ARDS. It is designed as an observational, cross sectional study of new cases of PARDS involving 5 continuous days of screening and patient enrollment, occurring every 2 months during 2016, and monthly in 2017 (10 total study weeks). Included patients will have a new diagnosis of PARDS during the study week. Data collection will concentrate on the first 3 days of PARDS diagnosis, and follow outcomes such as mortality and length of ventilation. The PARDIE study is comprised of a main study (V.0), and several ancillary or complementary studies. The ancillary studies are V.1, V.2, and V.3 which require additional data collection on patients already enrolled in V.0. These three ancillary studies do not require screening of additional patients not already included in V.0. Two complementary studies (V.4 and Cardiac PARDIE), require screening additional patients in the intensive care units, and have different inclusion and exclusion criteria. It is possible that some patients are first enrolled in V.4 (at risk for PARDS) and are subsequently enrolled in V.0. Patients enrolled in Cardiac PARDIE will not be enrolled in any of the other studies. All of the PARDIE investigations are designed to qualify for a waiver of informed consent, which will be sought from institutional review boards at participating hospitals.

## **Background**

Advances in transport, surgical, and medical care in the 1940's led to terms such as "wet lung," "DaNang lung," and "shock lung" to describe patients who died from severe hypoxia and had diffuse pulmonary edema at autopsy [1]. In 1967 Ashbaugh and colleagues described a case series of patients with severe acute hypoxemic respiratory failure, poor lung compliance and diffuse alveolar infiltrates on chest x-ray. Although there was an eleven year old among the twelve patients in the case series, they coined the term acute respiratory distress syndrome in adults, which they later called the adult respiratory distress syndrome [2, 3]. Because of clinical and histological similarities, the name adult respiratory distress syndrome was derived from the Idiopathic (or Infant) Respiratory Distress Syndrome. The adult respiratory distress syndrome was subsequently defined in 1988, and when it was revised in 1994 at the American-European Consensus Conference it was renamed the Acute Respiratory Distress Syndrome (ARDS) [4, 5].

There are currently two definitions of ARDS. The Berlin Definition was published after the 2011 Berlin ARDS Consensus Conference. While there has been some attempt to validate the Berlin Definition in children, it was not created with children in mind. Given substantial differences in the epidemiology and management of children with ARDS as compared with adults, the Pediatric Acute Lung Injury Consensus Conference (PALICC) was convened to develop a pediatric definition of ARDS [6], which was recently published [7, 8]. The PALICC definition of pediatric ARDS (PARDS) is shown in Figure 1 and the Berlin definition of ARDS is shown in Figure 2.

The Berlin and PALICC definitions of ARDS are similar in regards to (a) the development of signs and symptoms within 7 days of a clinical insult, and (b) development of pulmonary edema that is not fully explained by cardiac failure or fluid overload. Important differences between the Berlin and PALICC definitions are:

1. The PALICC definition does not require bilateral infiltrates on CXR.
2. The PALICC definition introduces use of pulse oximetry and provides criteria for  $SpO_2:FiO_2$  when  $PaO_2:FiO_2$  is unavailable.
3. The PALICC definition introduces use of oxygenation index (OI) or oxygenation-saturation index (OSI) to stratify severity groups instead of PF ratio with minimum Positive End Expiratory Pressure (PEEP).
4. The PALICC definition creates specific criteria to define PARDS in children with chronic lung disease and cyanotic heart disease.
5. The PALICC definition identifies a group of patients felt to be at risk for PARDS.

<b>Age</b>	Exclude patients with peri-natal related lung disease			
<b>Timing</b>	Within 7 days of known clinical insult			
<b>Origin of Edema</b>	Respiratory failure not fully explained by cardiac failure or fluid overload			
<b>Chest Imaging</b>	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
<b>Oxygenation</b>	<b>Non Invasive mechanical ventilation</b>	<b>Invasive mechanical ventilation</b>		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP $\geq 5$ cm H <sub>2</sub> O <sup>2</sup> PF ratio $\leq 300$ SF ratio $\leq 264$ <sup>1</sup>	4 $\leq$ OI < 8 5 $\leq$ OSI < 7.5 <sup>1</sup>	8 $\leq$ OI < 16 7.5 $\leq$ OSI < 12.3 <sup>1</sup>	OI $\geq 16$ OSI $\geq 12.3$ <sup>1</sup>
<b>Special Populations</b>				
<b>Cyanotic Heart Disease</b>	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. <sup>3</sup>			
<b>Chronic Lung Disease</b>	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. <sup>3</sup>			
<b>Left Ventricular dysfunction</b>	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: PALICC Definition of PARDS**

OI = oxygenation index = (FiO<sub>2</sub> \* mean airway pressure\*100) / PaO<sub>2</sub>

OSI = oxygen saturation index = (FiO<sub>2</sub> \* mean airway pressure\*100) /SpO<sub>2</sub>

<sup>1</sup> Use PaO<sub>2</sub> based metric when available. If PaO<sub>2</sub> not available, wean FiO<sub>2</sub> to maintain SpO<sub>2</sub>  $\leq$  97% to calculate OSI or SF ratio

<sup>2</sup> For non-intubated patients treated with supplemental oxygen or nasal modes of non-invasive ventilation see Figure 3 for At Risk Criteria

<sup>3</sup> ARDS severity groups stratified by OI or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease

<b>Acute Respiratory Distress Syndrome</b>	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging <sup>a</sup>	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 (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation <sup>b</sup>	
Mild	200 mm Hg < PaO <sub>2</sub> /FiO <sub>2</sub> $\leq$ 300 mm Hg with PEEP or CPAP $\geq 5$ cm H <sub>2</sub> O <sup>c</sup>
Moderate	100 mm Hg < PaO <sub>2</sub> /FiO <sub>2</sub> $\leq$ 200 mm Hg with PEEP $\geq 5$ cm H <sub>2</sub> O
Severe	PaO <sub>2</sub> /FiO <sub>2</sub> $\leq$ 100 mm Hg with PEEP $\geq 5$ cm H <sub>2</sub> O

Abbreviations: CPAP, continuous positive airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

<sup>a</sup> Chest radiograph or computed tomography scan.

<sup>b</sup> If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO<sub>2</sub>/FiO<sub>2</sub>  $\times$  (barometric pressure/760)].

<sup>c</sup> This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

**Figure 2: Berlin Definition of ARDS**

### 1. Bilateral Infiltrates

Bilateral infiltrates on plain film chest radiographs (CXR) are a requirement in both the AECC and Berlin definitions of ARDS in order to differentiate patients with diffuse alveolar damage from those with lobar or focal disease [2, 9]. The ARDS Definition Task Force attempted to address the problems of poor inter-observer reliability and poor sensitivity and specificity of CXR in adults by making the criterion more explicit, stating that the bilateral infiltrates should be consistent with pulmonary edema and not fully explained by effusions, lobar/lung collapse, or nodules/masses [9]. Pediatric data on whether this approach will be effective are lacking, leaving several important considerations:

(1) There is marked Inter-observer variability in CXR reading for diagnosing acute lung injury in children;

(2) In both adults and children, the CXR has low sensitivity for demonstrating alveolar consolidation as compared with chest computed tomography (CT), and there is evidence suggesting that lung inflammation may occur without evidence of consolidation on CT;

(3) The pathologic findings of diffuse alveolar damage characterizing ARDS are not homogeneous in either adults or children, and it is unclear whether bilateral versus unilateral disease is meaningful; and

(4) There is a lack of consistent evidence that bilateral CXR infiltrates contributes to risk stratification in either adult or pediatric patients with ARDS.

Therefore, the PALICC criterion for CXR findings includes the requirement for there to be **new** infiltrates consistent with acute pulmonary parenchymal disease, and recommends future studies to include standardized interpretation of chest imaging and for stratification of patients based on the presence or absence of bilateral infiltrates. There should also be a determination of optimal common training or automated methods to reduce inter-observer variability in the interpretation of chest imaging [8, 10-12].

### 2. SpO<sub>2</sub> based criteria

The ARDS Task Force considered the use of SpO<sub>2</sub> as an alternative to PaO<sub>2</sub> for the hypoxemia metric in the definition of ARDS, but SpO<sub>2</sub>/FiO<sub>2</sub> (SF) was not included due to the loss of specificity when the SpO<sub>2</sub> is ≥ 98%. Requiring arterial blood sampling to diagnose ARDS in children results in a 30-40% reduction in the number of patients who can be evaluated, and may introduce a selection bias for patients with cardiovascular dysfunction [13-15]. The SF ratio has a strong relationship with PaO<sub>2</sub>/FiO<sub>2</sub> (PF) [16, 17], and for most patients it is arguably best practice to turn down the FiO<sub>2</sub> if the SpO<sub>2</sub> is ≥ 98%. The guidelines generated from the PALICC group recommend reduction in FiO<sub>2</sub> if SpO<sub>2</sub> is ≥ 98% as part of routine clinical practice.

### 3. OI and OSI instead of PF ratio with minimum PEEP

There are important differences between pediatric and adult providers in ventilator management. Pediatric providers more commonly use pressure modes (including volume targeted modes such as PRVC) of ventilation, whereas adult providers are more likely to use volume modes of ventilation. This difference in practice between adult and pediatric providers is likely to be important to the way in which data are interpreted. In the pediatric patient population tidal volume [18] is the dependent variable, whereas pressure is the dependent variable in the adult patient population. In addition, adult providers more commonly employ the PEEP-FiO<sub>2</sub> titration ladder described in the landmark ARDSNet tidal volume study, whereas there is a high degree of variability in the use of PEEP by pediatric providers [14, 19, 20].

The Berlin definition of ARDS now requires a minimum level (5 cm H<sub>2</sub>O) of PEEP or CPAP. Several ventilator pressure criteria (PEEP ≥ 10, plateau pressure, and static lung compliance) were considered, but the ARDS Task Force found that these raised complexities without improving predictive validity in adults [9]. Due to the generally lower, and more variable use of PEEP by pediatric providers, PALICC has recommended the use of the oxygenation index (OI = (FiO<sub>2</sub> x mean airway pressure x 100) ÷ PaO<sub>2</sub>) for risk stratification of pediatric ARDS. Using derivation and validation datasets, OI was found to perform at least as good as PF in discriminating mortality of pediatric patients with ARDS [10]. Given the problems with using PaO<sub>2</sub> described above, PALICC also recommends that the oxygenation saturation index (OSI = (FiO<sub>2</sub> x mean airway pressure x 100) ÷ SpO<sub>2</sub>) be utilized when OI is not available. In a study of pediatric patients at Children's Hospital Los Angeles (CHLA), SF and OSI were found to discriminate mortality at least as well, if not better, than PF and OI [15].

### 4. Children with cardiac and pulmonary co-morbidities

Pediatric patients with severe chronic respiratory disease, cyanotic congenital heart disease and left ventricular cardiac dysfunction have been historically excluded from most pediatric studies of ARDS. Since these patients are certainly capable of developing ARDS, and since they are likely to be a vulnerable population, PALICC felt it important to provide diagnostic criteria for these patients [10]. However, there are no data to guide the assignment of severity criteria, and future studies are necessary to determine risk stratification criteria in these patients.

### 5. At-risk for PARDS

The use of nasal modes of non-invasive respiratory support has substantially increased in adult and pediatric ICUs as well as inpatient wards. These nasal modes of non-invasive respiratory support have potential to wash out anatomic dead space, provide effective CPAP, as well as deliver high amounts of supplemental oxygen. However, due to the inability to accurately determine the amount of effective CPAP or the percent inspired O<sub>2</sub> delivered by these devices, PALICC recommendations include a definition for patients at risk of PARDS [8, 10] (Figure 3).

<b>Age</b>	Exclude patients with peri-natal related lung disease	
<b>Timing</b>	Within 7 days of known clinical insult	
<b>Origin of Edema</b>	Respiratory failure not fully explained by cardiac failure or fluid overload	
<b>Chest Imaging</b>	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease	
<b>Oxygenation</b>	<b>Non Invasive mechanical ventilation</b>	
	Nasal mask CPAP or BiPAP	Oxygen via mask, nasal cannula or High Flow
	FiO <sub>2</sub> ≥ 40% to attain SpO <sub>2</sub> 88-97%	SpO <sub>2</sub> 88-97% with oxygen supplementation at minimum flow <sup>2</sup> : < 1 year: 2 L/min 1 – 5 years: 4 L/min 5 – 10 years: 6 L/min >10 years: 8 L/min
	<b>Invasive mechanical Ventilation</b>	
	Oxygen supplementation to maintain SpO <sub>2</sub> ≥ 88% but OI < 4 or OSI < 5 <sup>1</sup>	

**Figure 3 PALICC Definition for at risk of PARDS**

<sup>1</sup> If PaO<sub>2</sub> not available, wean FiO<sub>2</sub> to maintain SpO<sub>2</sub> ≤ 97% to calculate OSI

<sup>2</sup> Given lack of available data, for patients on an oxygen blender, flow for at risk calculation = FiO<sub>2</sub> \* FlowRate (L/min)  
(e.g. 6L/min flow at 0.35 FiO<sub>2</sub> = 2.1 L/min)

### **Significance**

The majority of the data of the epidemiology of ARDS in children was obtained using the AECC definition of ARDS. The requirement of arterial blood sampling to diagnose ARDS in children has likely introduced a substantial sampling error, resulting in an underestimation of the incidence of ARDS in children. The PALICC definition of PARDS was developed using pooled derivation data sets, and validated using 6 pediatric ARDS data sets [10]. Since the PALICC definition of PARDS was developed using retrospective data obtained using the AECC definition, a multicenter prospective study of the prevalence of new incident cases of PARDS is necessary to determine whether the PALICC definition of PARDS can be used to identify children with ARDS, and whether the hypoxemia severity classification effectively discriminates mortality (PARDIE V.0).

We expect that 30-50% more patients will be identified by the PALICC definition of PARDS as compared with the AECC/Berlin definitions of ARDS. Therefore, the epidemiology, risk factors for mortality and understanding of practice patterns of providers caring for PARDS patients are likely to be affected by the PALICC definition of PARDS. In order to determine future research priorities, it is important to determine risk factors for mortality in PARDS patients (PARDIE V.1) and variability in practice patterns based on PARDS severity (PARDIE V.1 and V.2). The removal of bilateral infiltrates from the definition of PARDS is one of the most controversial elements of the PALICC definition, so it is important to determine the inter-observer reliability in the interpretation and prognostic relevance of chest imaging findings on the outcome of PARDS (PARDIE V.3).

Identifying patients who are at risk of developing ARDS is important to develop therapeutic prevention strategies. Therefore, it is important to understand the feasibility of an ARDS prevention study by investigating the PALICC criteria for patients at risk for PARDS (PARDIE V.4).

Pediatric patients with acquired and congenital heart disease have been excluded from previous studies of ARDS. However, these patients have multiple risk factors for PARDS, and it is likely that they have increased risk of mortality. Therefore, it is important to describe the number and frequency of mechanically ventilated children with acquired and congenital heart disease who meet PALICC criteria for PARDS (Cardiac PARDIE).

## **Research Design and Methods**

### **Study Overview**

The Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study is designed as a multi-center international observational, cross sectional study of new cases of PARDS involving 5 continuous days of screening and patient enrollment, occurring every 2 months in 2016, and monthly in 2017 (10 total study weeks). Included patients will have a new diagnosis of PARDS during the study week. Data collection will concentrate on the first 3 days of PARDS diagnosis, and follow outcomes such as mortality and length of ventilation. The main goal of PARDIE is to better understand the implications of the new Pediatric Acute Lung Injury Consensus Conference (PALICC) definition of Pediatric ARDS on the incidence and epidemiology of Pediatric ARDS.

The PARDIE study is comprised of a main study (V.0), and several ancillary or complementary studies. The ancillary studies are V.1, V.2, and V.3 which require additional data collection on patients already enrolled in V.0. These three ancillary studies do not require screening of additional patients not already included in V.0. Two complementary studies (V.4 and Cardiac PARDIE), require screening additional patients in the intensive care units, and have different inclusion and exclusion criteria. It is possible that some patients are first enrolled in V.4 (at risk for PARDS) and are subsequently enrolled in V.0. Patients enrolled in Cardiac PARDIE will not be enrolled in any of the other studies. All of the PARDIE investigations are designed to qualify for a waiver of informed consent, which will be sought from institutional review boards at participating hospitals.

### **Study Dates**

The PARDIE study involves 5 continuous days of screening and patient enrollment. The study weeks are as follows:

- a. May 9-13, 2016
- b. July 11-15, 2016
- c. September 12-16, 2016
- d. November 14-18, 2016
- e. January 9-13, 2017
- f. February 13-17, 2017\*
- g. March 20-24, 2017
- h. April 17-21, 2017\*
- i. May 15-19, 2017\*
- j. June 12-16, 2017\*

\*The February 2017, April 2017, May 2017, and June 2017 study weeks are optional. Sites may choose not to participate in these additional study weeks.

## **PARDIE V.0: PARDS Epidemiology**

### PARDIE V.0 has 3 primary goals and objectives:

1. To determine the number and frequency of new cases of PARDS amongst PICU patients, and their respective outcomes, including ICU and hospital mortality
2. To evaluate how the PALICC recommended mild, moderate, and severe classification of PARDS performs in discriminating ICU and hospital mortality
3. To determine how the timing of hypoxemia metrics (OI, OSI, PF, SF) within the first three days of PARDS onset affects the discrimination ability of ICU and hospital mortality

### Screening

All patients admitted to a participating intensive care unit during a study day will be screened for eligibility based on the below inclusion and exclusion criteria.

### Inclusion Criteria

- Included patients must meet all 4 PARDS criteria below (Timing, Origin of edema, Chest imaging, Oxygenation)
  1. Hypoxemia within 7 days of a known clinical insult (PARDS risk factor)
  2. **AND** Respiratory failure not fully explained by cardiac failure or fluid overload
  3. **AND** Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease
  4. **AND** Minimal hypoxemia criteria based on mechanical ventilator support
    - a. Full face (oro-nasal) mask CPAP or BiPAP (minimal CPAP 5 cmH<sub>2</sub>O) with PaO<sub>2</sub>/FiO<sub>2</sub> (PF) ratio ≤ 300 **or** SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio ≤ 264 **or**
    - b. Invasive mechanical ventilation with Oxygenation Index ≥ 4 **or** Oxygen Saturation Index ≥ 5
- **AND** All diagnostic criteria for PARDS are met for the first time within the previous 24 hours (only new cases of PARDS)
- **AND** For children with chronic home mechanical ventilation, they must have an *acute deterioration in oxygenation* from their baseline

### Exclusion Criteria

- Patient is in the ICU in preparation for or recovering from cardiac intervention for the management of heart disease
- **OR** Patient has current cyanotic heart disease
- **OR** Patient's hypoxemia is explained by active perinatal related lung disease
- **OR** PARDS criteria met within 7 days of cardiopulmonary bypass
- **OR** Patient previously met PARDS criteria during this current illness > 24 hours prior to screening

### Patient Recruitment and Informed Consent

Waiver of informed consent is requested for all eligible patients. Waiver of consent is necessary for the scientific validity of the PARDIE study because the first goal of the study is to determine the number and frequency of new cases of PARDS amongst PICU patients, and their respective outcomes, including ICU and hospital mortality. This

requires inclusion of all patients who meet criteria for PARDS, not just patients who consent to enrollment. Selective inclusion of only patients who consent to the study will result in selection bias, and will not accurately represent the global burden of PARDS. There may not be time to approach families of patients who die quickly or who are most critically ill for consent. This will result in inaccurate estimates of mortality and PARDS incidence.

To protect patient privacy, personal identifying information will remain at the local institution participating in the study, and a unique study identification number will be assigned to each patient. All data transmitted outside the local institution will not contain any protected patient identifiers. All of the data collected in the PARDIE study is routinely available as part of clinical care, or exists in the medical record.

### Study Procedures

The PARDIE study will be conducted during pre-specified weeks of the year, with screening and enrollment Monday through Friday (5 days total in a week). Each morning of the study week, all patients in the ICU will be screened for eligibility. Patients who otherwise meet all PARDS criteria, but do not have a qualifying arterial blood gas, and do not have  $SpO_2 \leq 97\%$  with  $FiO_2$  of at least 0.35 will require bedside screening for eligibility. Research personnel will alert bedside providers if they feel a patient meets the above criteria. For these patients, bedside providers will be requested to wean the  $FiO_2$  until the  $SpO_2 \leq 97\%$ , or until the  $FiO_2$  is  $\leq 0.3$ .  $SpO_2/FiO_2$  ratios or Oxygen Saturation Index (OSI) will then be calculated to determine if the patient meets criteria for ARDS. Titration of  $FiO_2$  to achieve  $SpO_2 \leq 97\%$  is consistent with current evidence based guidelines, and represents standard practice in intensive care units. However,  $FiO_2$  is sometimes intermittently turned up for patients and providers need to be reminded to reduce  $FiO_2$  back down to maintain  $SpO_2 \leq 97\%$ . Turning down the  $FiO_2$  to achieve  $SpO_2 \leq 97\%$  poses no risk to the patient, and is explicitly recommended by current ARDS guidelines. Exclusion of these patients or requiring consent of these patients will compromise the validity of the study. The first goal of the study is to determine the number and frequency of new cases of PARDS amongst PICU patients, and their respective outcomes, including ICU and hospital mortality. This requires inclusion of all patients who meet criteria for PARDS. Selective inclusion of only patients who consent or who already have an  $SpO_2 \leq 97\%$  and  $FiO_2 > 0.35$  will result in selection bias, and will not accurately represent the global burden of PARDS. This will result in inaccurate estimates of mortality and PARDS incidence.

### Data Collection

There are three phases of data collection: at enrollment, daily for 3 days, and outcome (Hospitalization Summary) follow up. **See V.0 data elements list for all elements.**

Elements collected on enrollment include demographics, individual qualifying elements for the diagnosis of PARDS, patient co-morbidities, and PIM 3 score.

Daily (x 3 days) data surrounds ventilation mode, chest imaging, arterial blood gas results, and pulse oximetry results.  $SpO_2$  data will only be collected when  $SpO_2$  is  $\leq$

97%, and in line with current evidence based guidelines, bedside providers will be reminded to wean the  $\text{FiO}_2$  until the  $\text{SpO}_2 \leq 97\%$ , or until the  $\text{FiO}_2$  is  $\leq 0.3$ . Daily data will only be collected for patients who meet criteria for study defined respiratory support at the beginning of that day (invasive mechanical ventilation or non-invasive ventilation with minimal CPAP of 5  $\text{cmH}_2\text{O}$ ).

Hospitalization summary will be completed 90 days after enrollment in the study, or at hospital discharge or transfer, whichever comes first. Elements collected as part of the hospitalization summary include study dates and times in which the patient met PARDS criteria, data to calculate length of invasive and non-invasive ventilation, ventilator free days, mortality, and cause of death.

### Study Termination

The endpoint of the study for individual patients is 90 days after enrollment (met PARDS criteria) or hospital discharge/transfer, whichever comes first.

### Statistics and Analysis Plan

The three main questions for PARDIE V.0 will be used to drive the sample size estimates. The first question is largely descriptive, and is not associated with a hypothesis to test. The second question surrounds mortality discrimination between mild, moderate, and severe PARDS, and forms the basis for sample size estimates.

Existing data is limited with respect to the potential influence of pulse oximetry based criteria on overall mortality for PARDS. Based on the few published studies, it is anticipated that overall mortality may be lower for patients who meet PALICC PARDS criteria, compared to those who met AECC or Berlin criteria. This is largely explained by the selection bias that exists with arterial blood gas monitoring, which is frequently reserved for sicker patients or those with more cardiovascular instability. Looking at the three existing datasets (below), there may be limited discrimination of mortality between mild and moderate PARDS. This was also true with the external validation of the Berlin definition in adults. As such, the primary hypothesis is that the severe PARDS patients will have significantly higher mortality than the mild/moderate PARDS patients. This analysis will be tested with a chi-squared test. Based on the preliminary data presented below which likely underestimates PARDS mortality globally (data gathered in tertiary care children's hospitals), even with pulse oximetry criteria, we expect the mortality for severe PARDS patients to be  $\geq 22\%$ . We expect the mortality for mild/moderate patients to lie between 8-15%. We anticipate that 25% of the patients enrolled in the PARDIE study will fall into the severe PARDS group. Enrolling 200 patients in the severe PARDS group will allow us to identify a 9% mortality difference between mild/moderate PARDS and severe PARDS. While this is an observational study, enrolling  $> 800$  PARDS patients will allow us to detect this mortality difference, with the assumptions above. Hence the targeted sample size for the PARDIE study is 800 patients.

	Mild	Moderate	Severe
Mortality (validation set)	10%	20%	30%
Minimum N Needed (sig from prev)	199	294	294
Mortality (CHLA data with OSI)	8%	13%	30%
Minimum N Needed (sig from prev)	589	589	91
Mortality (CHOP data with OI)	5%	10%	20%
Minimum N Needed (sig from prev)	435	435	199

The third question surrounds timing of the hypoxemia metrics and discrimination of mortality. This will be performed through comparison of paired Areas under the Curve of the Receiver Operating Characteristic Plot (AUC of ROC) from hypoxemia metrics at PARDS onset, compared to those 24 hours after PARDS onset. Additional exploratory analysis will be performed looking at additional time points for the first 3 days after PARDS diagnosis. It is expected, based on preliminary data, that AUCs of ROC plots for these hypoxemia metrics against both ICU and hospital mortality will fall between 0.65-0.75. In this range, with the sample size above we will be able to detect a  $\geq 0.02$  difference in AUC of the ROC plot between paired samples.

## **PARDIE V.1: Risk Factors for Mortality in PARDS**

PARDIE V.1 has 2 primary goals and objectives:

1. To determine the risk factors for mortality in PARDS
2. To describe current practice regarding patient management stratified by PALICC mild, moderate, and severe classification of PARDS

### Inclusion Criteria

- Enrollment in V.0

### Exclusion Criteria

- None

### Patient Recruitment and Informed Consent

Identical to V.0.

### Study Procedures

For all patients enrolled in V.0, sites participating in V.1 will proceed with collection of the additional data elements described below.

### Data Collection

There are two phases of data collection for V.1: at enrollment and daily for 3 days. **See V.1 detailed data elements list.**

Elements collected on enrollment include additional demographics, PRISM III and PELOD scores, vasoactive medications, fluid intake and output, ventilator details, specific medications, and ancillary therapies for PARDS management.

Daily (x 3 days) data includes PELOD scores, vasoactive medications, fluid intake and output, ventilator details, specific medications, and ancillary therapies for PARDS management. Daily data will only be collected for patients who meet criteria for study defined respiratory support at the beginning of that day (invasive mechanical ventilation or non-invasive ventilation with minimal CPAP of 5 cmH<sub>2</sub>O).

### Study Termination

Identical to V.0.

### Statistics and Analysis Plan

It is anticipated that a subset of sites participating in V.0 will participate in V.1. For the first question, a multivariable logistic regression model will be created to identify variables with an independent association with mortality amongst PARDS patients, controlling for PARDS severity class. The second question is largely descriptive.

## **PARDIE V.2: Monitoring and Ventilator Management in PARDS**

### PARDIE V.2 has 2 primary goals and objectives:

1. To determine the association between bedside measures of disease severity and ventilator management and outcome in PARDS
2. To describe current practice for patient monitoring in PARDS and how this differs based on disease severity classification

### Inclusion Criteria

- Enrollment in V.0

### Exclusion Criteria

- None

### Patient Recruitment and Informed Consent

Identical to V.0

### Study Procedures

For all patients enrolled in V.0, sites participating in V.2 will proceed with collection of the additional data elements described below.

### Data Collection

There are three phases of data collection for V.2: at enrollment, daily every 6 hours for 3 days, and at extubation. **See V.2 detailed data elements list.**

Elements collected on enrollment include details surrounding intubation.

Daily (x 3 days, q 6 hours) data includes ventilator type, specific interventions, ventilator modes and level of support, ventilator settings, blood gas results, and results of other invasive or non-invasive monitoring (when available). Daily data will only be collected for patients who meet criteria for study defined respiratory support at the beginning of that day (invasive mechanical ventilation or non-invasive ventilation with minimal CPAP of 5 cmH<sub>2</sub>O).

Extubation data includes type of respiratory support used after extubation.

### Study Termination

Identical to V.0.

### Statistics and Analysis Plan

It is anticipated that a subset of sites participating in V.0 will participate in V.2. For the first question, a multivariable logistic regression model will be created to identify composite or timed variables from ventilator settings and patient monitoring which have an independent association with mortality amongst PARDS patients. The second question is largely descriptive.

### **PARDIE V.3: Chest Imaging in PARDS**

#### PARDIE V.3 has 3 primary goals and objectives:

1. To determine the prognostic relevance of chest imaging findings on outcome of PARDS, controlling for hypoxemia
2. To determine the inter-rater variability in the interpretation of chest imaging for PARDS amongst and between pediatric intensive care practitioners and radiologists
3. To gather electronic images of radiographs to develop and test automated methodologies to minimize variability

#### Inclusion Criteria

- Enrollment in V.0

#### Exclusion Criteria

- None

#### Patient Recruitment and Informed Consent

Identical to V.0.

#### Study Procedures

For all patients enrolled in V.0, sites participating in V.3 will proceed with collection of the additional data elements described below.

#### Data Collection

V.3 requires blinded interpretation of chest x-rays by two providers (one pediatric intensivist and one radiologist) at PARDS onset, and daily for 3 days (when available). If additional chest imaging (beyond chest x-ray) is available, then research personnel will ask a radiologist (pediatric if available), to fill out a case report form regarding interpretation of the imaging. **See V.3 detailed data elements list.**

For sites with capabilities to do so, de-identified chest x-ray images will be uploaded to the PARDIE server, linked by study number.

#### Study Termination

Identical to V.0.

#### Statistics and Analysis Plan

It is anticipated that a subset of sites participating in V.0 will participate in V.3. For the first question, multivariable logistic regression models will be created including individual hypoxemia metrics (OSI, OI, SF, PF) and the interpretation of bilateral versus unilateral infiltrates on CXR to examine if there is an independent association between bilateral infiltrates and mortality in PARDS. For the second question, individual data elements detailing interpretation of the CXRs will be compared between providers (radiologist versus intensivist), and kappa statistics will be generated for all elements, with particular attention to bilateral infiltrates.

**PARDIE V.4: At Risk for PARDS**PARDIE V.4 has 4 primary goals and objectives:

1. What is the rate at which PICU patients who meet “at risk” criteria convert to PARDS?
2. What is the difference in outcomes for PICU patients meeting “at risk” criteria who convert to PARDS as compared with patients meeting “at risk” criteria who do not convert to PARDS?
3. What are the risk factors for developing PARDS among patients meeting “at risk” criteria?
4. What percentage of patients meeting PARDS criteria also met “at risk” criteria during their hospitalization and where did this occur?

Screening

All patients admitted to a participating intensive care unit during a study day will be screened for eligibility based on the below inclusion and exclusion criteria.

Inclusion Criteria

- Included patients must meet all 4 at risk for PARDS criteria below (Timing, Origin of edema, Chest imaging, Oxygenation)
  1. Hypoxemia within 7 days of a known clinical insult (PARDS risk factor)
  2. **AND** Respiratory failure not fully explained by cardiac failure or fluid overload
  3. **AND** Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease
  4. **AND** Minimal hypoxemia criteria based on mechanical ventilator support
    - a. Nasal CPAP or BIPAP (or oronasal CPAP < 5cmH<sub>2</sub>O) with FiO<sub>2</sub> ≥ 0.4 to maintain SpO<sub>2</sub> 88-97%
    - b. **OR** Oxygen therapy (Mask, Nasal Cannula, High Flow Nasal Cannula) with minimal oxygen flow rate (based on age)\* to maintain SpO<sub>2</sub> 88-97%
      1. < 1 year of age: 2L/min
      2. 1- 5 years of age: 4L/min
      3. 5-10 years of age: 6L/min
      4. > 10 years of age: 8 L/min
    - c. **OR** Invasive mechanical ventilation with Oxygenation Index < 4 **or** Oxygen Saturation Index < 5
- **AND** All diagnostic criteria for at risk for PARDS are met for the first time within the previous 24 hours (only new cases of at risk for PARDS)

Exclusion Criteria

- Patient is in the ICU in preparation for or recovering from cardiac intervention for the management of heart disease
- **OR** Patient has current cyanotic heart disease
- **OR** Patient’s hypoxemia is explained by active perinatal related lung disease
- **OR** At risk for PARDS criteria met within 7 days of cardiopulmonary bypass

- **OR** Patient has previously met at risk for PARDS criteria during this current illness > 24 hours prior to screening
- **OR** Patient has previously met PARDS criteria during this current illness

#### Patient Recruitment and Informed Consent

Waiver of informed consent is requested for all eligible patients. Waiver of consent is necessary for the scientific validity of V.4 because the epidemiologic nature of the study mandates inclusion of all patients who meet at risk criteria for PARDS, not only patients who consent to enrollment. Selective inclusion of only patients who consent to the study will result in selection bias, and will not accurately represent the global burden of patients at risk for PARDS.

To protect patient privacy, personal identifying information will remain at the local institution participating in the study, and a unique study identification number will be assigned to each patient. All data transmitted outside the local institution will not contain any protected patient identifiers. All of the data collected in V.4 is routinely available as part of clinical care, or exists in the medical record.

#### Study Procedures

V.4 will run concurrently with V.0 during the same study weeks, and generally will involve different patients. A subset of patients who are first enrolled in V.4 may subsequently be included in V.0. In addition to screening for V.0, sites participating in V.4 will also screen all patients in the ICU who are on respiratory support with supplemental oxygen for V.4 eligibility. Patients who otherwise meet all at risk for PARDS criteria and do not have  $SpO_2 \leq 97\%$  while on supplemental oxygen will require bedside screening for eligibility. Research personnel will alert bedside providers if they feel a patient meets the above criteria. For these patients, bedside providers will be requested to wean the supplemental oxygen until the  $SpO_2 \leq 97\%$ , or until the  $FiO_2$  is  $\leq 0.3$  for non-invasive ventilation or high flow nasal cannula with an oxygen blender, or less than the pre-defined minimum liter per minute flow per age for those on supplemental oxygen therapy (or those on high flow nasal cannula without an oxygen blender) (see inclusion criteria above). Titration of oxygen to achieve  $SpO_2 \leq 97\%$  represents standard practice in intensive care units. However,  $FiO_2$  is sometimes intermittently turned up for patients and providers need to be reminded to reduce  $FiO_2$  back down to maintain  $SpO_2 \leq 97\%$ . Turning down the  $FiO_2$  to achieve  $SpO_2 \leq 97\%$  poses no risk to the patient, and is explicitly recommended by current ARDS guidelines. Exclusion of these patients or requiring consent of these patients will compromise the validity of the study. The study seeks to identify all patients who meet at risk for ARDS criteria in the ICU. Selective inclusion of only patients who consent or who already have an  $SpO_2 \leq 97\%$  and  $FiO_2 > 0.35$  will result in selection bias, and will not accurately represent the number of patients at risk for ARDS.

#### Data Collection

There are four phases of data collection: at enrollment, daily for 3 days, and outcome follow up (Hospitalization Summary). In addition, for sites concurrently enrolling in V.0

and V.4, all patients in V.0 will have an additional case report form for V.4 (retrospective evaluation of V.0 patients) **See V.4 data elements list.**

Elements collected on enrollment include demographics, individual qualifying elements for the diagnosis of at risk for PARDS, and patient co-morbidities.

Daily (x 3 days) data surrounds respiratory support, chest imaging, and vital signs (every 6 hours). SpO<sub>2</sub> data will only be collected when SpO<sub>2</sub> is  $\leq 97\%$ , and in line with current evidence based guidelines, bedside providers will be reminded to wean the oxygen until the SpO<sub>2</sub>  $\leq 97\%$  (as above).

Hospitalization summary will be completed 90 days after enrollment in the study, or at hospital discharge or transfer, whichever comes first. Elements collected as part of the hospitalization summary include study dates and times in which the patient met at risk for PARDS criteria, data to calculate length of invasive and non-invasive ventilation, whether the patient subsequently met PARDS criteria, ventilator free days, mortality, and cause of death.

Retrospective evaluation of V.0 patients will be applicable to all patients in V.0 from sites who are also participating in V.4. For these patients two additional questions are asked including whether the subject met at risk for PARDS criteria prior to meeting PARDS criteria, and where and when this at risk criteria was met (hospital location).

#### Study Termination

The endpoint of the study for individual patients is 90 days after enrollment (met at risk for PARDS criteria) or hospital discharge/transfer, whichever comes first.

#### Statistics and Analysis Plan

The analyses for V.4 are largely descriptive, so no specific sample size estimates have been generated. The analysis plan for question 1 is to describe the rate of conversion to PARDS amongst at risk patients. This will help determine the feasibility of a study on PARDS prevention targeting an intervention that reduces the rate of conversion to PARDS. Question 2 involves univariate analysis of mortality and ventilator free days between those who are at risk for PARDS and convert to PARDS compared to those who remain only at risk for PARDS. This will help determine whether the conversion to PARDS is a relevant surrogate outcome for mortality or ventilator free days if used in PARDS prevention study. Question 3 will involve creation of a multivariable model exploring the risk factors amongst at risk for PARDS patients to convert to PARDS. This will help refine potential interventions to prevent PARDS conversion. Analysis for question 4 will largely be descriptive in order to help determine the feasibility of performing a PARDS prevention study that targets a therapy which will start when the patient presents to the hospital.

## Cardiac PARDIE: PARDS Epidemiology in Cardiac Patients

### Cardiac PARDIE has 3 primary goals and objectives:

- 1 To describe the number and frequency of new cases of PARDS amongst mechanically ventilated patients with acquired and congenital heart disease who are greater than 7 days following cardiopulmonary bypass or cardiac ECMO
2. To describe the outcome (mortality and VFDs) for patients with acquired and congenital heart disease and PARDS who are greater than 7 days following cardio-pulmonary bypass or cardiac ECMO
3. To explore the use of objective criteria to decrease variability in potentially subjective clinical criteria for PARDS in children with acquired and congenital heart disease (LV dysfunction, acute deterioration in oxygenation not explained by underlying cardiac disease)

### Screening

All patients admitted to a participating intensive care unit during a study day will be screened for eligibility based on the below inclusion and exclusion criteria.

### Inclusion Criteria

- To be eligible for Cardiac PARDIE, patients must be a “Cardiac Patient.” “Cardiac Patient” is defined as
  - a. Any child in the ICU in preparation for or recovering from cardiac intervention (cath/surgery) for management of heart disease **OR**
  - b. Any child with an active diagnosis of cyanotic congenital heart disease. Cyanotic congenital heart disease is defined as
    1. Significant intra-cardiac mixing of blood flow / significant right to left shunt resulting in baseline saturations  $<90\%$ ; **OR**
    2. Ductal/prostaglandin dependent pulmonary or systemic blood flow; **OR**
    3. Single ventricle physiology (including Fontan)
- **AND** Hypoxemia within 7 days of a known clinical insult (PARDS risk factor)
- **AND** Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease
- **AND** Included patients must meet study defined hypoxemia based on ventilator support
  - a. Non-invasive ventilation with full face mask (minimum CPAP of 5 cmH<sub>2</sub>O) and  $FiO_2 \geq 0.4$  to maintain  $SpO_2 \leq 97\%$  and in the expected range for the patient’s anatomy **OR**
  - b. Invasive mechanical ventilation with minimum PEEP 5 cmH<sub>2</sub>O and  $FiO_2 \geq 0.4$  to maintain  $SpO_2 \leq 97\%$  and in the expected range for the patient’s anatomy
- **AND** All criteria are met for the first time within the previous 24 hours (only new cases of likely PARDS)

### Exclusion Criteria

- Patient’s hypoxemia is explained by active perinatal related lung disease

- **OR** Patient is within 7 days of cardiopulmonary bypass or cardiac ECMO
- **OR** Patient previously met PARDS criteria during this current illness > 24 hours prior to screening

#### Patient Recruitment and Informed Consent

Waiver of informed consent is requested for all eligible patients. Waiver of consent is necessary for the scientific validity of Cardiac PARDIE because the epidemiologic nature of the study mandates inclusion of all patients who potentially meet criteria for PARDS, not only patients who consent to enrollment. Selective inclusion of only patients who consent to the study will result in selection bias, and will not accurately represent the global burden of patients with cardiac disease and PARDS.

To protect patient privacy, personal identifying information will remain at the local institution participating in the study, and a unique study identification number will be assigned to each patient. All data transmitted outside the local institution will not contain any protected patient identifiers. All of the data collected in Cardiac PARDIE is routinely available as part of clinical care, is known by the bedside provider, or exists in the medical record.

#### Study Procedures

Cardiac PARDIE will run concurrently with V.0 during the same study weeks, but will involve different patients. No patients are anticipated to overlap between Cardiac PARDIE and V.0. Sites participating in Cardiac PARDIE will screen all “Cardiac Patients (defined above)” in the ICU who are invasively mechanically ventilated or on oro-nasal mask non-invasive ventilation with minimal CPAP of 5 cmH<sub>2</sub>O. Patients who otherwise meet all criteria and do not have SpO<sub>2</sub> ≤97% with FiO<sub>2</sub> of at least 0.35 will require bedside screening for eligibility. Research personnel will alert bedside providers if they feel the patient meets the above criteria. For these patients, bedside providers will be requested to wean the supplemental oxygen until the SpO<sub>2</sub> ≤97%, or until the FiO<sub>2</sub> is ≤ 0.3. Titration of oxygen to achieve SpO<sub>2</sub> ≤97% represents standard practice in intensive care units. However, FiO<sub>2</sub> is sometimes intermittently turned up for patients and providers need to be reminded to reduce FiO<sub>2</sub> back down to maintain SpO<sub>2</sub> ≤97%. Turning down the FiO<sub>2</sub> to achieve SpO<sub>2</sub> ≤97% poses no risk to the patient, and is explicitly recommended by current ARDS guidelines. Exclusion of these patients or requiring consent of these patients will compromise the validity of the study. The study seeks to identify all cardiac patients who may meet ARDS criteria. Selective inclusion of only patients who consent or who already have SpO<sub>2</sub> ≤97% and FiO<sub>2</sub> > 0.35 will result in selection bias, and will not accurately represent the number of cardiac patients with ARDS.

#### Data Collection

There are *two levels* of data collection for Cardiac PARDIE. The **first level** of collection will be performed for patients who meet all inclusion and no exclusion criteria above. All patients who meet these criteria will have **level 1 Cardiac PARDIE data collected**, which includes demographics, medical history, PARDS risk factors, and chest imaging. Subsequently, the clinical providers or PI will be asked additional questions to

determine whether further data collection is needed. If the clinical providers or PI believe the patient's respiratory failure is fully explained by cardiac failure or fluid overload **OR** they believe the acute deterioration in oxygenation is explained by underlying cardiac disease, then data collection is complete. If neither is true, then the **second level** of data collection is required. ***See Cardiac PARDIE data elements list for detailed description of level 1 and level 2 data.***

Elements collected as part of the **second level** include baseline data, daily data, and a hospitalization summary.

Baseline data includes individual qualifying elements for the diagnosis of PARDS, characteristics about the patient's baseline saturations, ventilator parameters at study enrollment, patient co-morbidities, and PIM 3 score.

Daily (x 3 days) data surrounds ventilation mode, chest imaging, arterial blood gas results, pulse oximetry results, and ventilator settings. SpO<sub>2</sub> data will only be collected when SpO<sub>2</sub> is ≤ 97%, and in line with current evidence based guidelines, bedside providers will be reminded to wean the FiO<sub>2</sub> until the SpO<sub>2</sub> ≤97%, or until the FiO<sub>2</sub> is ≤ 0.3. Daily data will only be collected for patients who meet criteria for study defined respiratory support at the beginning of that day (invasive mechanical ventilation or non-invasive ventilation with minimal CPAP of 5 cmH<sub>2</sub>O).

Hospitalization summary will be completed 90 days after enrollment in the study, or at hospital discharge or transfer, whichever comes first. Elements collected as part of the hospitalization summary include study dates and times in which the patient met PARDS criteria, data to calculate length of invasive and non-invasive ventilation, ventilator free days, mortality, and cause of death.

#### Study Termination

The endpoint of the study for individual patients who qualify for the second level of data collection is 90 days after enrollment (met PARDS criteria) or hospital discharge/transfer, whichever comes first.

#### Statistics and Analysis Plan

The analyses for Cardiac PARDIE are largely descriptive, so no specific sample size estimates have been generated. The analysis plan for question 1 is to report the rate of PARDS amongst cardiac patients. This will help determine the burden of PARDS in cardiac patients. Question 2 involves descriptive statistics of mortality and ventilator free days amongst cardiac patients with PARDS. Question 3 will involve examining whether objective data from echocardiography, cardiac catheterization, serum biomarkers, or ventilator support can identify patients who are likely to be diagnosed by clinicians as having PARDS (based on their answers to the questions about origin of edema and hypoxemia explained fully by underlying cardiac disease). In addition, if there are a sufficient number of deaths in this cohort, these factors in addition to ventilator settings and measures of hypoxemia will be used in an exploratory multivariable model examining association with mortality.

## References

1. Fishman, A.P., *Shock lung: a distinctive nonentity*. *Circulation*, 1973. **47**(5): p. 921-923.
2. Ashbaugh, D.G., et al., *Acute respiratory distress in adults*. *Lancet*, 1967. **2**(7511): p. 319-323.
3. Petty, T.L. and D.G. Ashbaugh, *The adult respiratory distress syndrome. Clinical features, factors influencing prognosis and principles of management*. *Chest*, 1971. **60**(3): p. 233-239.
4. Murray, J.F., et al., *An expanded definition of the adult respiratory distress syndrome*. *The American review of respiratory disease*, 1988. **138**(3): p. 720-723.
5. Bernard, G.R., et al., *The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination.*, in *American journal of respiratory and critical care medicine*. 1994. p. 818-824.
6. Thomas, N.J., P. Jouvett, and D. Willson, *Acute Lung Injury in Children-Kids Really Aren't Just "Little Adults"*. *Pediatric Critical Care Medicine*, 2013. **14**(4): p. 429-432.
7. Force, A.D.T., et al., *Acute respiratory distress syndrome: the Berlin Definition.*, in *JAMA : the journal of the American Medical Association*. 2012. p. 2526-2533.
8. Group, T.P.A.L.I.C.C., *Pediatric Acute Respiratory Distress Syndrome*. *Pediatric Critical Care Medicine*, 2015. **16**(5): p. 428-439.
9. Ferguson, N.D., et al., *The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material*. *Intensive Care Medicine*, 2012. **38**(10): p. 10.
10. Khemani, R.G., et al., *Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference*. *Pediatric Critical Care Medicine*, 2015. **16**(5\_suppl): p. S23-S40.
11. Zaglam, N., et al., *Computer-aided diagnosis system for the Acute Respiratory Distress Syndrome from chest radiographs*. *Computers in Biology & Medicine*, 2014. **52**: p. 41-8.
12. Zaglam, N., et al., *Inter-observer Variability for Radiography in Pediatric Acute Respiratory Distress Syndrome and Improvement with a Computer-Aided Diagnosis System*. *Austin Journal of Emergency and Critical Care Medicine*, 2015. **2**(3): p. 1-5.
13. Curley, M.A., et al., *Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial*. *JAMA*, 2005. **294**(2): p. 229-37.
14. Santschi, M., et al., *Acute lung injury in children: therapeutic practice and feasibility of international clinical trials*. *Pediatric Critical Care Medicine*, 2010. **11**(6): p. 681-689.
15. Khemani, R.G., et al., *Pulse oximetry vs. PaO<sub>2</sub> metrics in mechanically ventilated children: Berlin definition of ARDS and mortality risk*. *Intensive Care Medicine*, 2015. **41**(1): p. 94-102.

16. Khemani, R.G., et al., *Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the PaO<sub>2</sub>/fraction of inspired oxygen ratio in children*. Chest, 2009. **135**(3): p. 662-8.
17. Khemani, R.G., et al., *Comparison of SpO<sub>2</sub> to PaO<sub>2</sub> based markers of lung disease severity for children with acute lung injury*. Crit Care Med, 2012. **40**(4): p. 1309-16.
18. Vagima, Y., et al., *MT1-MMP and RECK are involved in human CD34+ progenitor cell retention, egress, and mobilization*. Journal of Clinical Investigation, 2009. **119**(3): p. 492-503.
19. Brower, R.G., et al., *Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome*. N Engl J Med, 2004. **351**(4): p. 327-36.
20. Khemani, R.G., et al., *Variability in usual care mechanical ventilation for pediatric acute lung injury: the potential benefit of a lung protective computer protocol*. Intensive Care Medicine, 2011. **37**(11): p. 1840-1848.