Acute Respiratory Distress Syndrome
Pathophysiology and Evidence-Based Management Strategies
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Disclosures
• None

Objectives
• Review pathophysiology of acute respiratory distress syndrome (ARDS)
• Describe latest definition and criteria for Pediatric Acute Respiratory Distress Syndrome (PARDS)
• Discuss evidence-based therapeutic management for PARDS

History: ARDS
• First defined in 1994 by the American European Consensus Conference (AECC)
  • Syndrome of inflammation and increased permeability in the lungs associated with a constellation of clinical, radiological, and physiologic abnormalities that cannot be explained by left atrial or pulmonary capillary hypertension
  • Acute lung disease with bilateral pulmonary infiltrates on chest radiograph, with a PaO2 to FiO2 ratio of ≤ 200. Must be acute onset, no evidence of left atrial hypertension

Khemani et al. Ped Crit Care Med. 2015

Definition: Pediatric ARDS (PARDS)
• A group of critical care investigators convened to establish a pediatric specific definition
• Charged to determine if Berlin Criteria for ARDS was applicable to children
• PICO method used to review literature/answer questions (P: Patient, problem or population; I – Intervention; C – Comparison, control; O: Outcome(s)
• Expert opinion

Khemani et al. Ped Crit Care Med. 2015

History: PARDS
• For years, the adult definition has been used for children with purposes of research, clinical care, and prognostication
• Berlin definition (2012), addressed limitations of prior definition, however, did not include pediatric considerations
• Shares characteristics with adult ARDS, though, differences in pediatric-specific practice patterns, comorbidities, and outcomes between adults and children

Khemani et al. Ped Crit Care Med. 2015
Definition: Pediatric ARDS (PARDS)

- **Lower age limit:** None
- **Though,** exclusion for causes of acute hypoxemia unique to prenatal conditions (e.g., lung injury from perinatal events, surfactant deficiencies...)
- **Upper limit:** No clear breakpoint between adolescents and young adults
- Future studies needed to evaluate potential age-dependent difference in pathophysiology of PARDS

Khemani et al. Ped Crit Care Med. 2015

Definition: Pediatric ARDS (PARDS)

- **Timing and Triggers:**
  - Symptoms of hypoxemia and radiographic changes must occur within 7 days of the clinical insult
  - Some etiologies are often associated with prompt development of ARDS (submersion injuries, transfusion associated lung injury, neurogenic pulmonary edema)
- **Coexistence with LV Failure/Dysfunction:**
  - If presence of LV failure/dysfunction, must fulfill all other PARDS criteria and new chest radiograph findings cannot be explained by LV failure or fluid overload

Khemani et al. Ped Crit Care Med. 2015

Definition: Pediatric ARDS (PARDS)

- **Radiographic findings:**
  - Chest radiograph with new infiltrate(s) consistent with acute pulmonary parenchymal disease
  - Future clinical trials for ARDS stratify for presence of unilateral or bilateral lung disease
  - Future studies needed to determine optimal training or effect of automated methodologies to reduce interobserver error in radiograph interpretation
  - Some studies have demonstrated that presence of bilateral infiltrates may have prognostic relevance

Definition: Pediatric ARDS (PARDS)

- **Respiratory Criteria for Disease Severity:**
  - Markers including
    - $\text{PaO}_2:\text{FiO}_2$ (PF) or $\text{SpO}_2:\text{FiO}_2$ ratios (SF)
    - Oxygen index (OI) $= \frac{\text{FiO}_2 \times MAP \times 100}{\text{PaO}_2}$
    - Oxygen saturation index (OSI) $= \frac{\text{FiO}_2 \times MAP \times 100}{\text{SpO}_2}$
  - Use of OI rather than PF ratio as primary metric of lung disease severity to define PARDS in patients receiving invasive mechanical ventilation
  - Use of PF ratio to diagnose PARDS in patients receiving non-invasive ventilation; minimum CPAP
  - Use OSI when OI not available
  - SF can be used when PF ratio not available
  - Trend towards less invasive monitoring

Khemani et al. Ped Crit Care Med. 2015

Definition: Pediatric ARDS (PARDS)

- **Coexistence with Cyanotic Congenital Heart Disease:**
  - Considered to have PARDS if fulfilling standard criteria (acute onset, known clinical insult, supportive chest radiographic findings supporting pulmonary parenchymal disease) and acute deterioration in oxygenation not explained by underlying congenital cardiac disease
  - *Not previously addressed in AECC or Berlin criteria*

Khemani et al. Ped Crit Care Med. 2015
Definition: Pediatric ARDS (PARDS)

- **Pre-existing chronic lung disease** treated with supplemental oxygen, non-invasive or invasive ventilation via trachestomy
- Considered to have PARDS if acute changes meeting standard PARDS criteria

Khemani et al. Ped Crit Care Med. 2015

Question

- Which of the following is a *direct* cause of PARDS?
  1. Sepsis
  2. Submersion injury
  3. Toxic ingestion
  4. Massive blood transfusion

Common Triggers

**Direct**
- Pneumonia
- Aspiration
- Submersion injury
- Severe thoracic trauma
- Reperfusion pulmonary edema (*e.g.* s/p lung transplant)
- Fat embolism
- Smoke inhalation

**Indirect**
- Sepsis
- Shock
- Multiple transfusions
- Severe non-thoracic trauma
- Pancreatitis
- Disseminated intravascular coagulation
- Toxic ingestion

Clinical Presentation

- Tachypnea
- Dyspnea
- Agitation/anxiety
- Hypoxia
- V/Q mismatch
- Reduced lung compliance
- Chest radiograph changes
- *Bronchoreactivity can be noted during and after recovery*
Question

A 2-year-old is on mechanical ventilation after smoke inhalation. Which ventilation monitoring parameter change would be consistent with development of PARDS for a child in pressure control ventilation?

1. Increased tidal volumes
2. Decreased tidal volumes
3. Decreased spontaneous breath rate
4. Increased auto PEEP

Phases of Lung Injury

**Exudative** – Acute onset of reduced pulmonary compliance, hypoxemia, tachypnea, chest radiograph – pulmonary edema

**Fibroproliferative** – Increased alveolar deadspace, chronic inflammation, scarring of pulmonary capillary bed, pulmonary hypertension

**Recovery** – Repair of alveolar epithelial barrier, improvements in pulmonary compliance, resolution of hypoxemia

ARDs Chest Radiograph

Typically...

- No cardiomegaly
- No Kerley B lines
- No pleural effusions
- Delay in CXR findings – 12 hours after insult

https://www.uichildrens.org
ARDS Chest Xray Progression

- 12 – 24 hours after insult:
  - Patchy alveolar infiltrates bilaterally
- 24 – 48 hours after insult:
  - Massive airspace disease bilaterally
- 5 – 7 days after insult:
  - Some clearing
  - Evaluate for superimposed pneumonia
- > 1 week
  - Coarse reticular pattern

ARDS Chest Radiograph

- 8 Days after insult:
  - Reticular pattern
  - Complex curvilinear; often diffuse
  - Further subdivision
  - Fine – ‘ground glass’ from thickened pulmonary interstitium
  - Medium – honeycombing appearance
  - Course – cystic spaces

Transfusion Associated Lung Injury

- 8 Days after insult:
  - Reticular pattern
  - Complex curvilinear; often diffuse
  - Further subdivision
  - Fine – ‘ground glass’ from thickened pulmonary interstitium
  - Medium – honeycombing appearance
  - Course – cystic spaces

The Pediatric Acute Lung Injury Consensus Conference Group

<table>
<thead>
<tr>
<th>Age</th>
<th>Exclude patients with peri-natal related lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Within 7 days of known clinical insult</td>
</tr>
<tr>
<td>Origin of Edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload</td>
</tr>
<tr>
<td>Chest Imaging</td>
<td>Chest imaging findings of new infiltrates consistent with acute pulmonary parenchymal disease</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Non invasive mechanical ventilation</td>
</tr>
<tr>
<td>Oxygen</td>
<td>{\text{FiO}_2 \geq 40% to attain \text{SpO}_2 \geq 97%}</td>
</tr>
<tr>
<td>NIV</td>
<td>nasal mask, nasal cannula or high flow</td>
</tr>
<tr>
<td>NICU, BiPAP, CPAP</td>
<td>\text{SpO}_2 \geq 97% with oxygen supplementation at minimum flow:</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>2 L/min</td>
</tr>
<tr>
<td>1 – 3 years</td>
<td>4 L/min</td>
</tr>
<tr>
<td>3 – 6 years</td>
<td>5 L/min</td>
</tr>
<tr>
<td>&gt;6 years</td>
<td>6 L/min</td>
</tr>
</tbody>
</table>

ARDS Chest CT Scan
Incidence
- Children: 2.1 – 12.8 per 100,000 person-years
  - U.S., Europe, Australia, New Zealand
- Adults: 17.9 – 81.0 per 100,000 person-years
  - U.S., Europe, Australia, New Zealand
- Males > females; though males do not have increased risk for mortality from ARDS

Khemani et al. Ped Crit Care Med. 2015

Question
- Which pre-existing illness in children has been associated with increased risk for ARDS?
  1. Asthma
  2. Laryngotracheomalacia
  3. Immunodeficiency
  4. Hepatitis B

Question
- Which of the following is the management priority for this patient?
  1. Prone positioning
  2. Exogenous surfactant administration
  3. Initiation of inhaled nitric oxide
  4. Continue current ventilator therapy with lung protective strategies

Case
15 y/o male with history of repaired atrial septal defect presents after motor vehicle accident with liver laceration and significant internal bleeding. He is post-operative day #1 and has required escalating ventilator settings overnight. He is now on FiO2 0.9 rate 18 pressure control 32 cm H2O pressure support 12 cm H2O, peep +12 cm H2O. His blood gas reveals a PaO2 of 52. What is his P/F ratio?

Question
- Which of the following is the management priority for this patient?
  1. Prone positioning
  2. Exogenous surfactant administration
  3. Initiation of inhaled nitric oxide
  4. Continue current ventilator therapy with lung protective strategies
### Management - General
- Numerous pharmacologic approach studies in adults
- Few, extensively explored in pediatrics. In part, due to lower incidence/mortality associated with ARDS
- Also, pediatric heterogeneity of underlying disease can vary greatly between infants and children
- May affect clinical features, response to therapy
- PARDs therapy based largely on adult data and anecdotal experience from pediatric critical care experts

### Management – Nitric Oxide
- **What is nitric oxide?**
  - It is synthesized in the vascular endothelium by NO synthase
  - Main effect:
    - Relaxation of smooth muscle by increasing intracellular cyclic guanosine monophosphate
- **Action**:
  - Local and short
  - Vasodilation primarily occurs in areas adequately ventilated; blood shunted away from areas not well ventilated
  - Reduces V/Q mismatch; reduces deadspace ventilation and increasing oxygenation

#### Recommendations
- iNO not recommended for routine use in PARDs
- May be considered in patients with documented pulmonary hypertension or severe right ventricular dysfunction
- May be considered as a rescue from or bridge to extracorporeal membrane oxygenation
- When in use; serial assessment of benefit to minimize toxicity.
- Elimination of use if no effect

Tamburro et al. Ped Crit Care Med. 2015

### Management – Surfactant
- **Surfactant**
  - Complex substance produced in the lungs; 6 lipids and 4 proteins; lipoprotein
  - Produced by Type II alveolar cells
  - Reduces surface tension of fluid in lungs; helps to reduce collapse of alveoli. Maximizes surface area available for gas exchange. Increases pulmonary compliance
  - Endogenous production begins in fetus
  - *Can also be synthetically manufactured*

#### Recommendations
- Not recommended as routine therapy in PARDs
- Further investigations should focus on populations most likely to benefit from this therapy

Tamburro et al. Ped Crit Care Med. 2015
Management – Prone Positioning

• Several mechanisms of its benefit have been proposed to improve oxygenation and outcomes
  • Has been shown to be safe
  • Short term benefits in oxygenation
  • No difference in ventilator, time to recovery from lung injury, or all cause mortality
• Recommendations
  • Not recommended as routine therapy in PARDS
  • Consider as an option in severe PARDS
  • Further pediatric study is warranted

Tamburro et al. Ped Crit Care Med. 2015

Management – Endotracheal Suctioning

• Essential in maintaining a patent airway
• Recommendations
  • Maintaining clear airway is essential in PARDS patients
  • Must be performed with caution to minimize risk of derecruitment
  • Insufficient data to support either open or closed suctioning; minimize potential for derecruitment
  • Routine instillation of normal saline prior to endotracheal suctioning is not recommended; may be used for tenacious secretions

Tamburro et al. Ped Crit Care Med. 2015

Management – Chest Physiotherapy (CPT)

• Efficacy has not been tested in an RCT
  • No published case series or observational data
• Recommendation
  • Insufficient data to recommend CPT as standard of care in PARDS

Tamburro et al. Ped Crit Care Med. 2015

Management - Corticosteroids

• The inflammatory process in PARDS has prompted an interest in anti-inflammatory therapies, including steroid therapy
• Available pediatric data; limited to case series
• No available RCTs investigating use of steroids in PARDS
  • Often used in daily pediatric critical care
• Adult studies fail to demonstrate clear benefit
• Recommendation
  • Routine use of corticosteroids not recommended
  • Future studies needed to identify populations likely respond to this therapy and appropriate dosing

Tamburro et al. Ped Crit Care Med. 2015

Management – Other therapies

• Inhaled prostaglandin I2; natural pulmonary vasodilator (epoprostenol or iloprost)
  • Similar approach as inhaled NO
  • No data to support
• Inhaled β2-agonists
  • Have not been studied in pediatrics
  • Discouraged in adult population
• Heliox
  • Experimentally; found to attenuate inflammatory effects of mechanical ventilation
  • Has not been studied in PARDS

Tamburro et al. Ped Crit Care Med. 2015
Management – Other Therapies

- N-acetylcysteine
  - Potent antioxidant agent
  - May be considered as therapeutic option; though, little pediatric data exists
  - No positive data supporting its use in adult ARDS
- Iprotropium bromide, dornase alpha, plasminogen activators, fibrinolytics, or other anticoagulants – not tested through RCTs

Recent Corticosteroid Study

- Single Center prospective observational study
- Patients meeting criteria for ARDS (Berlin 2012 & AECC 1994)
- N = 282
- 160 patients (60%) received steroids for > 24 hours while ventilated (5% hydrocortisone, 4% methylprednisolone)
- Results: Patients receiving steroids > 24 hours; fewer ventilator free days, longer duration of ventilation

Ventilatory Support

- Essential in the management of critically ill children
- May cause inflammation and lung injury
- Advocated management strategies include: modes that limit alveolar stretch, permissive hypercapnia, positive end expiratory pressure, recruitment maneuvers.
- Pediatric outcome data is sparse.

Consensus recommendations

- Use of cuffed endotracheal tubes in conventional ventilatory modes
- Uncuffed tubes can be considered when using HFOV to augment ventilation if MAP can be maintained
- Oxygenation and ventilation goals titrated based on perceived risks of toxicity
  - Oxygen saturations 92-97% for PEEP ≤10 cm H2O
  - Oxygen saturations 88-92% for PEEP > 10 cm H2O
  - When oxygen saturations < 92%, monitoring of central venous saturation and markers of oxygen delivery
- Permissive hypercapnia for moderate-to-severe PARDS to limit ventilatory induced lung injury; pH 7.15-7.30
- Bicarbonate supplementation not routinely recommended
**HFOV – Hematopoietic Cell Transplant Recipients**

- Comparison of conventional ventilation with HFOV in children after hematopoietic cell transplant with severe PARDS
- 12 centers in US
- 222 children in database; 85 managed w/ HFOV
- Survivors transitioned to HFOV earlier in course with lower OI

Rowan et al. Resp Care. 2018, 63(4)

**Adherence to Lung-Protective Mechanical Ventilation in PARDS**

- Descriptive post-hoc analysis
- 26 PICUs
- 315 children with PARDS
- Low tidal volume ventilation underused in first 24 hours
- Age and severity of illness not associated with adherence to low tidal volume ventilation
- Obese children less likely to receive low tidal volume ventilation

Ward et al. Pediatric Crit Care Med.

**Mortality**

- Lower in clinical trials
- Children: 18-27%
- Adults: 27-45%
- Some data from Australia suggests that adult and pediatric mortality may be more similar (35%)
- Some data suggests that incidence increases with advancing age
- Disparities in mortality: Black and Hispanic patients increased risk for mortality compared to Caucasian PARDS patients
  - Perhaps due in part to common polymorphism of the Duffy minor blood group type

Khemani et al. Ped Crit Care Med. 2015

**Outcomes - PARDS**

- Prospective multicenter observational trial
- 3 general PICUs; Brazil
- Children 1 month – 15 years of age with acute lung injury (ALI) or ARDS that developed at least 12 hours after invasive mechanical ventilation
- N = 3046; 84 with ALI or ARDS
- Logistic regression to explore relationship between death and independent variables

Panico et al. Ped Crit Care Med. 2015
Outcomes - PARDS

**TABLE 4. Association Between Potential Predictive Variables and Mortality, Including the Airway Pressure Gradient on Day 1 in the Model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate OR (95% CI)</th>
<th>P for Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of organ dysfunctions at admission</td>
<td>2.06 (1.20–3.60)</td>
<td>0.009</td>
</tr>
<tr>
<td>Pediatric Risk of Mortality score</td>
<td>1.01 (0.99–1.10)</td>
<td>0.867</td>
</tr>
<tr>
<td>Airway pressure gradient on day 1</td>
<td>1.10 (1.00–1.28)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

OR = odds ratio.


Outcomes – Fluid Balance

- Conclusions
  - PARDS – complex in need of multimodal therapy
  - Pediatric literature is sparse
  - Fluid overload associated with worse clinical outcomes (e.g. fewer VFDs, worse oxygenation)
  - **Early** fluid overload main influence
  - Further research needed – diuretics and renal replacement therapies in early PARDS


Outcomes – Red Blood Cell Administration


Association between tidal volumes adjusted for ideal body weight and outcomes in PARDS

Conclusions

- PARDS may be triggered by several pulmonary and extrapulmonary causes
- New PARDS definition can assist in identifying patients meeting criteria for PARDS
- Management focused on supportive therapies; additional studies are needed to identifies optimal management strategies