Pediatric ARDS: What’s New, PEEPs?

UTHSCSA Pediatric Grand Rounds
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Got PEEP?

Disclosures

• I have no financial relationships to disclose.

History

• “Acute Respiratory Distress in Adults” by Ashbaugh in Lancet in 1967
• 12 adult patients with clinical and pathologic symptoms similar to infant respiratory distress syndrome
• “Positive end-expiratory pressure was most helpful in combating atelectasis and hypoxemia.”

Lancet 1967 Aug 12;2(7511):319-23

Definition

The American-European Consensus Conference Definitions of ALI and ARDS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Timing</th>
<th>PaO2/FiO2</th>
<th>CXR</th>
<th>PWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>Acute onset</td>
<td>≤ 300</td>
<td>Bilateral infiltrates</td>
<td>≤ 18mmHg or the absence of clinical evidence of left atrial hypertension</td>
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<tr>
<td>ARDS</td>
<td>Acute onset</td>
<td>≤ 200</td>
<td>Bilateral infiltrates</td>
<td>≤ 18mmHg or the absence of clinical evidence of left atrial hypertension</td>
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Berlin Criteria

The Berlin Definition of Acute Respiratory Distress Syndrome

<table>
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<th>Category</th>
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<tr>
<td>Timing</td>
<td>Within 1 week of a known clinical insult or new/worsening respiratory symptoms</td>
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<tr>
<td>Chest imaging</td>
<td>Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules</td>
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<tr>
<td>Origin of edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (echo) to exclude hydrostatic edema if no risk factor present</td>
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<tr>
<td>Oxygenation</td>
<td>Mild: PaO₂/FiO₂ ≤ 300mmHg with PEEP or CPAP ≥ 5mm H₂O&lt;br&gt;Moderate: 200mmHg &lt; PaO₂/FiO₂ ≤ 300mmHg with PEEP or CPAP ≥ 5mm H₂O&lt;br&gt;Severe: PaO₂/FiO₂ ≤ 200mmHg with PEEP ≥ 5mm H₂O</td>
</tr>
</tbody>
</table>

Pediatric ARDS Criteria

- Pediatric Acute Lung Injury Consensus Conference
- Substitutes oxygenation index (OI) or oxygenation saturation index (OSI) for P/F ratio
- Allows for “pulmonary parenchymal disease” instead of bilateral infiltrates on chest imaging
- Allows for coexisting LV dysfunction, cyanotic heart disease, and chronic lung disease

Pathogenesis of ARDS

Endothelial and Epithelial Injury

- Alveolar-capillary barrier formed by 2 cellular layers: alveolar epithelium and vascular endothelium
- Increased permeability allows influx of protein-rich fluid into air spaces
- Epithelial injury impedes removal of edema fluid from the alveolar space
- Alveolar type II cell injury impedes surfactant production and turnover
- Activation of inflammatory cascade

Role of Cytokines

- Activated macrophages secrete proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8)<br>  - Local actions stimulate cytokines and activate neutrophils
- Neutrophils adhere to injured endothelium and marginate into the air spaces<br>  - Release oxidants, proteases, leukotrienes, and other proinflammatory molecules

Early Lung Injury

Furhman Ch 52: ARDS in Children
Role of Ventilator Induced Lung Injury

- Mechanical ventilation causes injury via
  - Volutrauma/Barotrauma
  - Atelectrauma
  - Biotrauma

Preventing Overdistension and Collapse Injury

- Add PEEP
- Limit TV
- Limit distending pressure

Resolution of Lung Injury

- Alveolar edema is resolved by the active transport of Na from air spaces into interstitium
- Insoluble proteins are removed by endocytosis and transcytosis, by alveolar epithelial cells, and by phagocytosis
- Type II cells proliferate to cover the denuded basement membrane and differentiate into type I cells to restore normal architecture and function
- New blood vessels are formed due to vascular endothelium growth factor to restore normal gas exchange

Fibrosing Lung Injury

- Progression to fibrotic lung injury occurs 5-10 days after the onset of ARDS
- Alveolar spaces are filled with fibroblasts and procollagen III peptide
- Mechanisms of resolution are unclear, but may involve apoptosis, antiinflammatory cytokines and proteases, and environmental and genetic factors

Clinical Features of ARDS
CXR

Incidence
- Difficult to measure due to changing definitions
- Prior to AECC definition, pediatric incidence was 1-4% of all PICU admissions
- Based on AECC definition, pediatric incidence is 1.3-4% of all PICU admissions
- Newer definitions with non-invasive criteria may over-estimate incidence

Etiology
- Direct lung injury
  - Pneumonia
  - Aspiration
  - Lung contusion
  - Hydrocarbon ingestion
  - Smoke inhalation
  - Sickle cell disease
- Indirect lung injury
  - Sepsis
  - Multiple emergent transfusions
  - Submersion injury

Phases
- Acute or exudative phase
  - 0-3 days
- Sub-acute or fibroproliferative phase
  - 4-10 days
- Chronic or fibrotic phase
  - > 10 days

Acute Phase
- Endothelial and epithelial injury with activation of the inflammatory cascade
- Tachypnea, dyspnea, agitation, and hypoxemia
- CXR shows diffuse bilateral alveolar opacities
- CT shows mix of abnormal dense lung regions and more functional lucent regions

Fibroproliferative Phase
- Proliferation of type II pneumocytes and fibroblasts
- Hyaline membranes worsen gas exchange
- Decreased lung compliance due to progressive fibrosis
- PEEP effects oxygenation to a lesser extent
- CO2 retention
Fibrotic Phase

- Does not occur in all patients
- Remodeling by collagenous tissue, arterial thickening, and obliteration of pre-capillary vessels
- Cystic lesions develop
- Pulmonary hypertension may develop due to changes in pulmonary vasculature

http://www.studyblue.com/notes/note/n/v-pulmonary-pathology-li/deck/1204974

Imaging of ARDS Phases

Outcomes

- Pediatric mortality 10-15%
- 500-2000 deaths annually in US
- Long term morbidity in adults includes
  - Chronic hypoxia
  - Weakness
  - Cognitive defects
  - Decreased QOL
- No long term data in pediatrics

Crit Care Med 2009;37(8):2448-2454

Predictors of Mortality

- Hypoxia severity at presentation is a strong predictor of mortality in pediatric ARDS
  - OI > 13 had 36% mortality vs OI < 13 (20%)
- Multi-organ failure is a strong predictor of mortality in ARDS

Crit Care Med 2009;37(8):2448-2454

Therapies

- Mechanical Ventilation Strategies
- Pharmacologic Therapies
- Mechanical Therapies

Mechanical Ventilation

- Add PEEP
- Limit distending pressure
- Limit TV
Noninvasive Ventilation

- Theoretical benefits include less sedation requirement, decreased complications
- In adults with ARDS, 50% failure rate of NIV
- No good data in pediatrics
- If limited to single organ failure, probability of NIV success is 86%
- Consider in selected patients

Low Tidal Volume Ventilation

- ARDSNet trial in 2000 in adults
- “Open lung strategy”
  - Tidal volumes 6-8ml/kg
  - PEEP minimum 5
- Study ended early due to increased mortality and ventilator-free days

Permissive Hypercapnea

- To avoid increasing ventilator support to injurious settings, may tolerate higher PCO₂ and lower pH
- ARDSNet trial tolerated arterial pH > 7.15
- Consensus for pediatrics:
  - Arterial pH goal > 7.3
  - No long-term data on cognitive effects of high PCO₂ in pediatrics

High Frequency Oscillation Ventilation

- CPAP with a “wiggle”
- High frequency, very low tidal volumes

HFOV

- As a rescue therapy, it has been associated with higher MAP, improved oxygenation, and reduced need for supplemental O₂ at 30 days
- Adult studies have shown no benefit (and even harm)
APRV

• Preliminary adult data shows APRV is no worse than ARDSNet protocol for ARDS
• Case reports only in pediatrics

Pharmacologic Therapies

Surfactant

• Produced by type II alveolar cells
• Disrupted production in ARDS
• Good data for treatment of infant RDS

Nature Medicine 2010;16:1078-79

Surfactant

• Adult studies are negative
• Early small pediatric studies were promising
• Larger pediatric RCTs:
  – Lucinactant improved oxygenation but no change in mortality or ventilator free days
  – Calfactant showed no improvement in oxygenation or mortality and was stopped for futility

Crit Care 2007;11:R66
Pediatr Crit Care Med 2013;14(7):S57-S65

Steroids

• Area of interest due to the large inflammatory component of ARDS
• Meduri studies showed benefit from treating early ARDS with low-dose methylprednisolone
• Adult dosing protocol with slow taper over 1 month

JAMA 1998;280(2):159-65
Chest 2007;131(4):954-963

Steroids

• High dose corticosteroids are not effective at preventing ARDS in at-risk patients
• ARDSNet trial on corticosteroids after 7 days of ARDS showed no benefit
  – Increased mortality if initiated after 14 days
• No pediatric data

NEJM 2006;354:1671-1684
Inhaled Nitric Oxide

- Pulmonary vascular vasodilator
- Theoretical benefits
  - Increase blood supply to open alveoli to improve V/Q matching

iNO

- Improved oxygenation transiently in the first 24 hours of use
- No improvement in mortality in adults or children
- No increase in ventilator free days
- Expensive!

Sedation

- Sedation is important to maintain ventilator synchrony
- No data to support specific regimens, but less sedation predicts shorter weaning from ventilation
- Neuromuscular blockade has been associated with critical illness myopathy with significant morbidity

Fluid Management

- Restrictive fluid management protocol in adults shows increased ventilator free days and oxygenation
- This has not been shown in children

Transfusion Goals

- Theoretically, maximizing adequate oxygen carrying capacity in the face of hypoxemia will improve oxygen delivery
- In adults, oxygen consumption in severe ARDS is independent of changes in oxygen delivery
- In critically ill children, a target Hb of 7 is as safe as Hb of 10

Mechanical Therapies
Partial Liquid Ventilation

- Perfluorocarbon to provide gentle ventilation
- Theoretical benefits:
  - Oxygen reservoir
  - Alveolar recruitment and lavage
  - Improved V/Q matching
  - Anti-inflammatory
- Few human studies with no benefit, possible harm

Prone Positioning

- West zones redistribute in supine patients
  - Zone 3 is most dorsal
  - Zone 1 is most ventral
- Theoretical benefits of proning
  - Improve V/Q matching
  - Relieve pressure from heart

Extracorporeal Membrane Oxygenation

- “Lung bypass”
- Typically used as a rescue therapy for severe ARDS that has failed more conservative therapy
- Earlier ECMO has better outcomes

Future Research

- Standardized definition for pediatrics
- Advances in ECMO technology
- Trials in process or beginning soon:
  - Steroids in early ARDS
  - Statins in ALI
  - Nebulized heparin for ALI
  - ASA to prevent ALI
  - Keratinocyte growth factor in ALI
  - Vitamin D to prevent ALI
  - Interferon-b in ARDS