Hipoxemia refractaria: estrategia de manejo

Raffo Escalante-Kanashiro MD
<table>
<thead>
<tr>
<th>Year</th>
<th>Onset</th>
<th>Chest Radiograph</th>
<th>Etiology</th>
<th>Failure of Oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>12 patients Lancet</td>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashbaugh</td>
<td></td>
<td></td>
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<tr>
<td>1994</td>
<td>A=Adult</td>
<td>Acute</td>
<td>Bilateral infiltrates</td>
<td>Acute Lung Injury: PaO2:FiO2 Ratio &lt; 300</td>
</tr>
<tr>
<td>American/European Consensus Statement</td>
<td></td>
<td></td>
<td>Not secondary to heart failure: PA Pressure &lt; 18 or no LA HTN</td>
<td>ARDS :PaO2:FiO2 Ratio &lt; 200</td>
</tr>
<tr>
<td>2012</td>
<td>Within 1 week of inciting event</td>
<td>Bilateral infiltrates not explained by effusions or atelectasis</td>
<td>NOT cardiac failure or fluid overload by some objective measure (eg, echocardiogram)</td>
<td>Mild ARDS: PF ratio 201-300 on CPAP/PEEP ≥ 5</td>
</tr>
<tr>
<td>Berlin Criteria</td>
<td></td>
<td></td>
<td></td>
<td>Moderate ARDS: PF 101-200 on PEEP ≥ 5</td>
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<td></td>
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<td></td>
<td></td>
<td>Severe ARDS: PF ≤ 100 on PEEP ≥ 5</td>
</tr>
<tr>
<td>2015</td>
<td>Pediatric Specific</td>
<td>Unilateral or bilateral infiltrates not explained by effusions or atelectasis</td>
<td>NOT cardiac failure or fluid overload by some objective measure (eg, echocardiogram)</td>
<td>Not intubated: CPAP ≥ 5 with PF ≤ 300 or SF ≤ 264</td>
</tr>
<tr>
<td>PALICC-PARDS</td>
<td></td>
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<td>Mild ARDS: OI 4 to 8; OSI 5 to 7.5</td>
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<tr>
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<td></td>
<td></td>
<td>Moderate ARDS: OI 8 to 16; OSI 7.5 to 12.3</td>
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<td></td>
<td>Severe ARDS: OI ≥ 16; OSI ≥ 12.3</td>
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</table>
Phases of ARDS

- Acute - exudative, inflammatory (0 - 3 days)
- Subacute - proliferative (4 - 10 days)
- Chronic - fibrosing alveolitis (> 10 days)
Phases of ARDS
Severe refractory hypoxemia may develop in a subset of patients with severe ARDS. Severe ARDS is often associated with refractory hypoxemia, and early identification and treatment of hypoxemia is mandatory.
Strategy of *permissive hypoxemia* (SaO2 82–88 %)

The “classical” concept of oxygen delivery/consumption
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

Pediatric Crit Care Med 2013;14(4):429-32
<table>
<thead>
<tr>
<th>Tiempo</th>
<th>Dentro de los primeros 7 días tras producirse una alteración clínica conocida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origen Edema</td>
<td>Insuficiencia respiratoria no explicada completamente por insuficiencia cardíaca o sobrecarga de líquidos</td>
</tr>
<tr>
<td>Rx tórax</td>
<td>Hallazgo de nuevo(s) infiltrado(s) compatibles con afectación aguda del parénquima pulmonar</td>
</tr>
</tbody>
</table>

**Oxigenación**

<table>
<thead>
<tr>
<th>Ventilación mecánica No Invasiva</th>
<th>Ventilación mecánica Invasiva</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDRA-P (Sin estratificación de gravedad)</td>
<td>Leve</td>
</tr>
<tr>
<td>—</td>
<td>4 ≤ IO &lt; 8</td>
</tr>
<tr>
<td>Ventilación (doble nivel) con mascarilla facial completa o CPAP ≥5cmH2O</td>
<td>5 ≤ IOS &lt; 7.5¹</td>
</tr>
<tr>
<td>PF ≤ 300</td>
<td>SF ≤ 264 ¹</td>
</tr>
</tbody>
</table>

**Poblaciones especiales**

<table>
<thead>
<tr>
<th>Cardiopatía cianótica</th>
<th>Mismos criterios que los arriba descritos para edad, tiempo, origen del edema y Rx de tórax junto a un deterioro agudo de la oxigenación no explicado por la cardiopatía subyacente.³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfermedad crónica pulmonar</td>
<td>Mismos criterios que los arriba descritos para edad, tiempo, y origen del edema junto a Rx tórax compatible con nuevo infiltrado y deterioro agudo en la oxigenación basal que cumplan los criterios de oxigenación arriba descritos.³</td>
</tr>
<tr>
<td>Disfunción ventricular izquierda</td>
<td>Mismos criterios que los arriba descritos para edad, tiempo y origen del edema junto a Rx tórax compatible con cambios correspondientes a un nuevo infiltrado más deterioro agudo de la oxigenación que además cumple con los criterios anteriores y no se explica por la disfunción ventricular izquierda.</td>
</tr>
</tbody>
</table>

The Pediatric Acute Lung Injury Consensus Conference Group
Pediatr Crit Care Med 2015; XX:00–00
| **Age** | Exclude patients with peri-natal related lung disease |
| **Timing** | Within 7 days of known clinical insult |
| **Origin of Edema** | Respiratory failure not fully explained by cardiac failure or fluid overload |
| **Chest Imaging** | Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease |

<table>
<thead>
<tr>
<th><strong>Oxygenation</strong></th>
<th><strong>Non Invasive mechanical ventilation</strong></th>
<th><strong>Invasive mechanical Ventilation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal mask CPAP or BiPAP</td>
<td>Oxygen via mask, nasal cannula or High Flow</td>
<td>Oxygen supplementation to maintain $\text{SpO}_2 \geq 88%$ but OI &lt; 4 or OSI &lt; 5$^1$</td>
</tr>
</tbody>
</table>
| $\text{FiO}_2 \geq 40\%$ to attain $\text{SpO}_2$ $88$-$97\%$ | $\text{SpO}_2$ 88-97% with oxygen supplementation at minimum flow$^2$:  
  < 1 year: 2 L/min  
  1 – 5 years: 4 L/min  
  5 – 10 years: 6 L/min  
  >10 years: 8 L/min |
ARDS with refractory hypoxemia
\[ \text{PaO}_2/\text{FiO}_2 < 100 \]
\[ \text{PaO}_2 < 60 \text{ mmHg} \]
\[ \text{SaO}_2 < 88\% \]

**Ventilatory setting I**
- Volume controlled
- \( V_T \) 6ml/kg PBW
- \( P_{\text{plat}} < 30 \text{ cmH}_2\text{O} \)
- \( I : E = 1:1 \)
- RR = 20-30/min
- Heated humidifier

**Ventilatory setting II**
- \( P\text{EEP} \)
- ‘high’ \( P\text{EEP}/\text{FiO}_2 \)- combination
- Titration to pressure-volume curve
- \( P_{\text{v}} \) stress index
- Recruitment

**Positioning**
- Prone position (latest ≤ 48 h after onset)
- 16 h sessions repeated

**Supportive measures**
- Neuro-muscular blockade ≤ 48 h
- Adapted sedation:
  - RASS-score
  - Consider ASB ≥ 48 h
- Consider PV on individual basis
  - Negative fluid balance
  - Consider early hemofiltration

**Infection control**
- Source:
  - CT-scan (whole body?)
  - Blood culture
  - Bronchoscopy
  - Lung biopsy (?)

**Consider**
- Atypical
- Fungal
- Virus
  - β-D-glucan galactomannan

**Early broad-spectrum antibiotics**
**Antifungal, virostatics, VAP-bundle**
→ after diagnosis: de-escalation

Late (≥ 7 d) or focal ARDS:
- No OLA

Early or diffuse ARDS:
- One OLA

Hemodynamics ↓
Right ventricle ↓
A precise definition of life-threatening hypoxemia is not identified. Typical clinical determinations are: arterial partial pressure of oxygen < 60 mmHg and/or arterial oxygenation < 88 % and/or the ratio of PaO2/FIO2 < 100.
ARDS is characterized by acute onset respiratory failure associated with severe hypoxemia $\text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg}$ and bilateral pulmonary infiltrates not fully explained by heart failure or fluid overload. The Berlin criteria, ARDS may be classified as mild ($\text{PaO}_2/\text{FiO}_2$ ranging from 201 to 300mmHg), moderate ($\text{PaO}_2/\text{FiO}_2$ ranging from 101 to 200mmHg) or severe ($\text{PaO}_2/\text{FiO}_2 \leq 100\text{mmHg}$). ARDS continues to be correlated with high mortality rates, which may reach 36% to 44% in specialized centers, despite the progress made in treatment in recent decades.

A review defined **refractory hypoxemia** as PaO2/FIO2 100 mm Hg, inability to keep plateau pressure below 30 cm H2O despite a VT of 4 mL/kg ideal body weight, development of barotrauma, and oxygenation index 30

Severe hypoxemic respiratory failure: part 1: ventilatory strategies.
The oxygenation index predicts poor outcome from lung injury in the neonatal and pediatric population and its utility is also evidenced in adults with ARDS. Oxygenation index links the severity of hypoxemia and mean airway pressure to a single variable:

**Oxygenation index = (FIO2 x mean airway pressure x 100)/PaO2**

Oxygenation index predicts outcome in children with acute hypoxemic respiratory failure.
Am J Respir Crit Care Med 2005;172(2):206-211.
Ventilator induced lung injury:

• High FiO2 > 60%: leading to oxygen toxicity
• Barotrauma: Alveolar injury from exposure to excessive pressures
• Volutrauma: Repetitive opening and closing of alveoli causing shear stress and triggering further inflammation
“Pressure-controlled ventilation (PCV) probably reduces ICU mortality (32%, 95% CI 27% to 37%) compared with volume-controlled ventilation (VCV) (38%; moderate-quality evidence), and probably does not differ from VCV in terms of mortality in hospital or at 28 days (moderate-quality evidence); however, the numbers evaluated were small, and further research may change these estimates”

Mortality from ARDS is usually due to multi-organ failure, often from sepsis; however, 10–15% of patients die of refractory hypoxemia.
• Entirely supportive
  • Fluid management (dry lungs are happy lungs)
  • Open lung ventilation strategy

• Controversies
  • Role of non-invasive ventilation
  • Continuous neuromuscular blockade
  • Prone positioning
  • Surfactant
  • Corticosteroids
  • Inhaled Nitric Oxide
  • Unconventional mechanical ventilation (HFOV, HFPV, APRV)
  • ECMO
• Use enough PEEP (range from 8 to 20) to allow for FiO2 <0.6.
• A higher FiO2 exposes the lung to oxygen toxicity; therefore all efforts should be made to decrease the FiO2 <0.6.
• The PEEP should be 2-3 cmH2O greater than the lower inflection point of a static Pressure-Volume curve and should be associated with the best compliance.
• Lower oxygen saturations of 88%-95% or paO2 55-80mmHg can be accepted in order to minimize oxygen toxicity.

NEJM 2000 ARDS Network study
• Low tidal volume with a goal of 6 ml/kg should be used. This goal tidal volume can be decreased if plateau airway pressures are > 30 cm H2O
• Therefore goal plateau pressure is <30. The preferred mode of ventilation is time cycled, pressure regulated, and volume controlled

NEJM 2000 ARDS Network study
• Set a ventilatory rate to achieve pH 7.3-7.45. Often, permissive hypercapnia with a pH down to 7.2 is allowed to minimize ventilator induced lung injury.
• Be vigilant of I-time, inspiratory time, while setting the rate. A longer I-time optimizes pulmonary recruitment.
The ARDS Network study demonstrated that the above strategy compared to traditional ventilatory methods decreased mortality (31% vs. 39.8%), increased ventilator free days, and decreased plasma interleukin concentrations in adult patients with ARDS. A pediatric study has not been performed to date.
Fluid Administration

The patient should be aggressively fluid resuscitated for any signs / symptoms of shock in order to optimize end organ perfusion.

Once hemodynamic stability is achieved, fluid administration should be minimized to decrease the alveolar-capillary leak and pulmonary edema.
Continuous neuromuscular blockade
- ACURASYS trial of 48hr cisatracurium infusion v placebo
- Adult patients PF < 150 (moderate/severe ARDS)
- Cisatracurium infusion reduced mortality (32% v 41%), and reduced barotrauma
- Hypothesized that NMB improved patient-ventilator synchronization

Prone positioning
- PROSEVA trial of prone positioning (16 hours/day) v placebo
- Adult patients PF < 150 for 12-24h
- Proning reduced mortality (24% v 41%)
- ***Pediatric prone positioning trial stopped early for futility
  - No change in mortality but subsequent study demonstrated improved oxygenation

Papazian et al, *NEJM* 2010
Guerin et al, *NEJM* 2013
Prone Positioning

The greatest effects are achieved when patients are maintained prone for 12 hours or longer and oxygenation improves in 60-70% of patients.
Severe hypoxemia: which strategy to choose

Non-Invasive vs Invasive ventilation

Assess the severity of hypoxemia
(PEEP 5 cmH₂O FiO₂ 100%)

Mild
PaO₂/FiO₂ >200

Moderate
200<PaO₂/FiO₂<100

Severe
PaO₂/FiO₂ <100

Lung CT scan or lung ultrasound to assess lung recruitability

Optimize PEEP and lung recruitment
Use low tidal volume ventilation
Insure adequate gas exchange
Minimize VILI by monitoring the transpulmonary pressure or driving pressure
Always check hemodinamics

Avoid patient ventilator dyssynchrony by NMBAs

Apply prone position
Consider ECMO
Lung-recruitment maneuvers

Lung-recruitment maneuvers transiently increase transpulmonary pressure and open atelectatic alveoli, thus improving gas exchange.

Include sustained high-pressure inflation, intermittent and extended sighs, intermittent PEEP increases, and pressure control with PEEP

Anesthesiology 2002;96(4):795-802
What makes the PEEP "optimal"? The setting is said to be optimal when:

- The oxygenation is maximised
- There is minimal end-expiratory atelectasis (i.e. maximal end-expiratory recruitment)
- There is minimal end-inspiratory overdistension
• PEEP is a way to regain FRC
Individualized PEEP Setting in Subjects With ARDS: A Randomized Controlled Pilot Study
**Upper inflection point:** Pressure at which there is regional overdistension

**Lower inflection point:** Minimum pressure required for alveolar recruitment

- Peak airway pressure
- Tidal volume
- "Beaking": overdistension
- PEEP
- Alveolar recruitment and airway resistance
- Optimal compliance
- Alveolar overdistension
Recruitment manoeuvre: Oxygen saturation increases

Drop in saturation indicates derecruitment at this level of PEEP

Optimal open-lung level of PEEP

Stepwise decrease of PEEP while watching the saturation
Table 1. Modalities to Treat Refractory Hypoxemia in Patients With Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Risks and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung-recruitment maneuvers</td>
<td>Well tolerated, generally safe</td>
<td>Improvements transient</td>
<td>Contraindications: hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk of barotrauma</td>
</tr>
<tr>
<td>Airway pressure-release ventilation</td>
<td>Improved pulmonary mechanics, gas exchange, hemodynamics, less sedation</td>
<td>Theoretical risk of large pleural pressure swings</td>
<td>Theoretical risk: large tidal volume could increase risk of ventilator-induced lung injury</td>
</tr>
<tr>
<td>High-frequency oscillatory ventilation</td>
<td>May minimize atelectrauma</td>
<td>Concern about higher inflammation markers</td>
<td>Theoretical risk: lung inflammation</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>Homogeneous distribution of ventilation</td>
<td>Variable response, resource-intensive</td>
<td>Risks: loss of airway, vascular catheter, or chest drain; pressure ulcers; cardiac arrest</td>
</tr>
<tr>
<td>Inhaled nitric oxide, prostacyclin</td>
<td>Reduces right-ventricular afterload</td>
<td>Cost, delivery technologies</td>
<td>Inhaled nitric oxide risks: renal dysfunction, methemoglobinemia, reactive nitrogen species, rebound pulmonary hypertension</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>Can provide complete ventilatory and cardiovascular support</td>
<td>Cost, resource utilization, limited availability</td>
<td>Risks: numerous, including bleeding, infection, stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraindications: numerous</td>
</tr>
<tr>
<td>Intervention</td>
<td>Special Considerations</td>
<td>Supporting Evidence</td>
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<td>--------------------------------------------------</td>
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<tr>
<td>Heavy sedation and neuromuscular blockade</td>
<td>Consider for patient-ventilator asynchrony, Low cost and widely available, Risk of delirium from heavy sedation, Risk of prolonged weakness from neuromuscular blockade</td>
<td>8, 13, Adjusted HR, 0.68 (0.48-0.98)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Higher positive end-expiratory pressure or recruitment maneuvers</td>
<td>Easily done with conventional mechanical ventilators, Low cost and widely available, Risk of barotrauma and hypotension</td>
<td>14-17, Adjusted RR, 0.90 (0.81-1.00)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Prone positioning</td>
<td>No special equipment required, Low cost and widely available, Risk of local complications (eg, pressure sores, facial edema), Difficulty performing routine nursing care while patient is prone</td>
<td>11, 18-20, RR, 0.84 (0.74-0.96)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>High-frequency oscillatory ventilation</td>
<td>Consider early application if oxygenation improves with higher positive end-expiratory pressure or recruitment maneuvers, Requires special ventilator and expertise</td>
<td>21-23, RR, 0.77 (0.61-0.98)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>Consider if associated pulmonary hypertension, Change in dose-response curve over time, May not be widely available, Expensive</td>
<td>24-27, None</td>
<td></td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>Ability to use lower tidal volumes and airway pressures for lung recovery, Requires systemic anticoagulation, Expensive, Highly invasive, Requires expertise</td>
<td>10, 28, 29, RR, 0.69 (0.05-0.97)&lt;sup&gt;f&lt;/sup&gt;</td>
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</tr>
</tbody>
</table>
VMI:

Tubo Traqueal: Se recomienda tubo traqueal con cuff con un nivel de fuga del 10% para asegurar presiones o volumen durante la VMI.

Se sugiere Presión Control.

Se recomienda utilizar un volumen tidal (4-8 mL/kg en base a predicción de peso corporal). Se recomienda considerar percentil 50 P/T.

PEEP: se recomienda un rango de 5-15 cm H2O con titulación de FiO2.

Se sugiere utilizar la tabla de relación PEEP/FiO2, pero sólo orientadora y referencial.

Se sugiere limitar presión plateau a 28-32 cm H2O con un promedio de 30 cm H2O.
Se sugiere utilizar estrategia de hipercapnia permisiva con un valor pH no menor de 7.25 e inestabilidad hemodinámica, con metas de SPO2 de 88-92% si el PEEP es ≥ 10 cm H2O.

Se sugiere que la diferencial de presión (driving pressure: presión plateau - PEEP) de preferencia no debe ser mayor a 15 cm H2O.

Se recomienda de preferencia evitar inversión de la relación I: E.

Se sugiere hacer maniobras de reclutamiento después de cada aspiración si el circuito es abierto.

Monitoreo:
Nivel recomendado:
CO2 a un nivel de pH>7.25

PO2: podríamos aceptar más de 55-80 estable hemodinámico y Hb >7
SPO2: podríamos aceptar valores de 88-92%
Estabilidad Hemodinámica en rangos no menor a 5to percentil para la edad.

Imágenes: Ecografía, Radiología, Tomografía

Se recomienda ventilación en decúbito prono, según respuesta del paciente.

VAFO: se sugiere inicio con un parámetro de presión plateau es mayor de 28 a 30.

Se recomienda: BH negativo es lo ideal en ARDS con estabilidad hemodinámica.

Destete y liberación de VMI: seguir plan delineado en la UCI cuando se revierta condiciones que condujeron a VMI y ante resolución de curso de PARDS.