ACS Questions – October 2012

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Ann Arbor, MI
### Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Timing</th>
<th>Within 1 week of a known clinical insult or new or worsening respiratory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest imaging&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules</td>
</tr>
<tr>
<td>Origin of edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present</td>
</tr>
<tr>
<td>Oxygenation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>200 mm Hg &lt; $\text{PaO}_2/\text{FiO}_2$ ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H$_2$O&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Abbreviations:** CPAP, continuous positive airway pressure; $\text{FiO}_2$, fraction of inspired oxygen; $\text{PaO}_2$, 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: [$\text{PaO}_2/\text{FiO}_2 \times (\text{barometric pressure}/760)$].

<sup>c</sup>This may be delivered noninvasively in the mild acute respiratory distress syndrome group.
<table>
<thead>
<tr>
<th></th>
<th>AECC Definition</th>
<th>AECC Limitations</th>
<th>Addressed in Berlin Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Acute onset</td>
<td>No definition of acute(^4)</td>
<td>Acute time frame specified</td>
</tr>
<tr>
<td>ALI category</td>
<td>All patients with (\text{PaO}_2/\text{FiO}_2 &lt; 300) mm Hg</td>
<td>Misinterpreted as (\text{PaO}_2/\text{FiO}_2 = 201-300), leading to confusing ALI/ARDS term</td>
<td>3 Mutually exclusive subgroups of ARDS by severity ALI term removed</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>(\text{PaO}_2/\text{FiO}_2 \leq 300) mm Hg (regardless of PEEP)</td>
<td>Inconsistency of (\text{PaO}_2/\text{FiO}_2) ratio due to the effect of PEEP and/or (\text{FiO}_2)(^5)-(^7)</td>
<td>Minimal PEEP level added across subgroups FiO(_2) effect less relevant in severe ARDS group</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Bilateral infiltrates observed on frontal chest radiograph</td>
<td>Poor interobserver reliability of chest radiograph interpretation(^8),(^9)</td>
<td>Chest radiograph criteria clarified Example radiographs created(^a)</td>
</tr>
<tr>
<td>PAWP</td>
<td>(\text{PAWP} \leq 18) mm Hg when measured or no clinical evidence of left atrial hypertension</td>
<td>High PAWP and ARDS may coexist(^10),(^11) Poor interobserver reliability of PAWP and clinical assesses of left atrial hypertension(^12)</td>
<td>PAWP requirement removed Hydrostatic edema not the primary cause of respiratory failure Clinical vignettes created(^a) to help exclude hydrostatic edema</td>
</tr>
<tr>
<td>Risk factor</td>
<td>None</td>
<td>Not formally included in definition(^4)</td>
<td>Included When none identified, need to objectively rule out hydrostatic edema</td>
</tr>
</tbody>
</table>

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; \(\text{FiO}_2\), fraction of inspired oxygen; \(\text{PaO}_2\), arterial partial pressure of oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.

\(^a\)Available on request.
Question 1

All of the following have been demonstrated as beneficial effects of inhaled nitric oxide in adult ARDS patients **EXCEPT**:

A. Significant increase in PaO$_2$
B. Reduced mortality in adult ARDS
C. Decreased pulmonary arterial pressures
D. Improved right ventricular function
Question 1

All of the following have been demonstrated as beneficial effects of inhaled nitric oxide in adult ARDS patients EXCEPT:

A. Significant increase in PaO₂

B. Reduced mortality in adult ARDS

C. Decreased pulmonary arterial pressures

D. Improved right ventricular function
Inhaled Nitric Oxide and ARDS

NO is a selective pulmonary vasodilator that acts on the endothelial surface of the lung to produce regional vasodilation in ventilated lung units, resulting in improved right ventricular function.

NO improves oxygenation in ALI and ARDS, but has no effect on the duration of ventilatory support or mortality.

Although current cumulative evidence from clinical trials suggests that NO has no place in the routine therapy of patients with ARDS, short-term physiologic improvements may be crucial for patient survival in severe cases for whom refractory hypoxemia or pulmonary hypertension are major clinical problems.

In these limited situations, NO may have a role as salvage therapy, as a component of a multimodal approach that includes other strategies such as high-frequency oscillation and prone positioning.
Inhaled Nitric Oxide and ARDS: Results of Largest Meta-Analysis

Oxygenation 12 - 24 hrs
RR 1.13, CI 1.04 – 1.23

All-cause Mortality
RR 1.10, CI 0.94 – 1.30

Included 12 trials and 1237 patients
Adhikari NK et al. BMJ 2007 Apr 14;334(7597):779
Rescue Strategies in ARDS

Inhaled NO as Rescue for Severe ARDS
Question 2

Which of the following factors has the greatest impact on improving oxygenation in HFOV use in adult patients with ARDS?

A. Increased mean airway pressure
B. Decreased Hertz
C. Increased inspiratory time
D. Decreased power
Question 2

Which of the following factors has the greatest impact on improving oxygenation in HFOV use in adult patients with ARDS?

A. Increased mean airway pressure
B. Decreased Hertz
C. Increased inspiratory time
D. Decreased power
HFOV Protocols

**HIGH FREQUENCY OSCILLATORY VENTILATION OF THE ADULT PATIENT PROTOCOL**

F. Raise, or ensure that, the head of bed is set at 30 degrees

G. **INITIATE HFOV WITH THE FOLLOWING SETTINGS**
   1. $\text{FiO}_2$: 1.0
   2. Frequency: 5 Hz (300 bpm)
   3. Bias flow: 30 Lpm
   4. % Inspiratory Time: 33%
   5. Power Setting: Start at 6.0 and adjust to achieve an adequate wiggle (from clavicle to mid-thigh).
   6. Mean airway pressure ($\text{mPaw}$): 5 cmH$_2$O above mean airway pressure reading on the conventional mechanical ventilator.
   7. Set humidifier temperature to 38.5-39 degrees Celsius.

H. Perform a recruitment maneuver (see Appendix 1)

I. Create a partial cuff leak
Protocol for HFOV in Adults

**HFOV Quick Guide**

**Management of Ventilation**

Overall goal: Maintain pH in the target range at the minimum tidal volume. This is achieved by favoring higher frequencies over lower ΔP. This goal is also promoted by accepting mild respiratory acidosis rather than attempting to normalize pH.

Monitor:
- Obtain ABG at least 30 minutes after each change in settings.
- Check ABG BID in patient on stable settings.

Target pH: 7.25-7.35
Target f: 12 Hz

Initial settings:
- f = 5 Hz
- ΔP – PaCO2 on conventional ventilator + 20

Subsequent adjustments:
- pH in target range
  - Increase f and increase ΔP as follows:
    a) Increase f in increments of 1-2 Hz to max. of 12 Hz
    b) If pH falls below acceptable range at any f, increase ΔP in increments of 5 cmH2O to max. of 90 cmH2O

- pH too high (Correct metabolic alkalosis, if indicated)
  - Increase f in increments of 1-2 Hz to max. of 12 Hz, then
  - Decrease ΔP in 5 cmH2O increments to minimum of 20.

- pH too low (Correct metabolic acidosis, if indicated)
  (Consider possible pneumothorax, partial endotracheal tube occlusion, derecruitment)
  a) Increase ΔP in increments of 5 cmH2O until 90 cmH2O, then
  b) Add 5 cmH2O cuff leak, then
  c) Decrease f by 1 Hz increments to minimum of 3 Hz.

1 A 5 cmH2O cuff leak is produced by deflating the endotracheal tube cuff until mPaw falls by 5 cmH2O, then increasing bias flow rate to restore MAP to initial value.

**Management of Oxygenation**

Overall goal: Increase lung recruitment while avoiding overdistension; balance risks of overdistension versus oxygen toxicity. Mean airway pressure (mPaw) is used to recruit lung. Increased mPaw is favored over increased FiO2 unless patients have circulatory failure. Threshold for overdistension is unknown, but it may be more likely at mPaw > 35 cmH2O.

Monitor:
- SpO2 or PaO2: Observe SpO2 changes 5-10 minutes after a change in ventilator settings. Check ABG twice daily.

Target:
- PaO2: 55-80 mmHg or SpO2 88-95%; use PaO2 for decisions if only one is out of target range.

Initial settings and adjustments:
- mPaw = mPaw on conventional ventilator + 5 cmH2O, but do not exceed 35 cmH2O
- FiO2 = 1.0
- If oxygenation is below target, increase mPaw in 5 cmH2O increments to maximum of 45 cmH2O. Consider recruitment 1-2 maneuvers.
- If oxygenation is above target, decrease FiO2 to reach a FiO2/mPaw combination on scale

Subsequent adjustments:
- **Oxygenation in target range**
  - No change required
  - **Oxygenation above the target range**
    - Decrease down FiO2/mPaw scale in 1-2 step increments
    - Increase up FiO2/mPaw scale in 1-2 step increments
  (Consider recruitment maneuvers)
  (Higher mPaws may depress venous return; assure adequate volume.)
  (At mPaw > 35 or FiO2 > 0.9, consider prone positioning or iNO)

2 A recruitment maneuver consists of stopping oscillator and elevating mPaw to 45 cmH2O. Maintain for 40-60 seconds. Monitor closely for hypotension or desaturation. Return to desired settings and restart oscillator.
### HFOV Meta-analysis - Oxygenation

- PaO$_2$/FiO$_2$ ratio on days 1 to 3.

- HFOV increased PaO$_2$/FiO$_2$ ratio by 16% to 24% compared with conventional mechanical ventilation

**Table:**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>High frequency oscillation</th>
<th>Conventional mechanical ventilation</th>
<th>Ratio of means (95% CI)</th>
<th>Weight (%)</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derdak 2002</td>
<td>59</td>
<td>54</td>
<td>19.0</td>
<td>1.15</td>
<td>(0.96 to 1.37)</td>
</tr>
<tr>
<td>Shah 2004</td>
<td>15</td>
<td>13</td>
<td>13.2</td>
<td>1.60</td>
<td>(1.25 to 2.07)</td>
</tr>
<tr>
<td>Bollen 2005</td>
<td>35</td>
<td>23</td>
<td>13.4</td>
<td>1.08</td>
<td>(0.84 to 1.38)</td>
</tr>
<tr>
<td>Papazian 2005</td>
<td>13</td>
<td>13</td>
<td>10.0</td>
<td>1.05</td>
<td>(0.76 to 1.43)</td>
</tr>
<tr>
<td>Dernoy 2007</td>
<td>13</td>
<td>15</td>
<td>11.0</td>
<td>1.48</td>
<td>(1.11 to 1.99)</td>
</tr>
<tr>
<td>Mentzelopoulos 2007</td>
<td>27</td>
<td>27</td>
<td>21.5</td>
<td>1.35</td>
<td>(1.16 to 1.56)</td>
</tr>
<tr>
<td>Samransamrujkit 2005</td>
<td>7</td>
<td>9</td>
<td>12.0</td>
<td>1.06</td>
<td>(0.80 to 1.39)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>169</td>
<td>154</td>
<td><strong>100.0</strong></td>
<td><strong>1.24</strong></td>
<td>(1.10 to 1.40)</td>
</tr>
</tbody>
</table>

**Test for heterogeneity:** $t^2=0.01$, $\chi^2=10.96$, $df=6$, $P=0.09$, $I^2=46\%$

**Test for overall effect:** $z=3.60$, $P<0.001$

<table>
<thead>
<tr>
<th>Day 2</th>
<th>High frequency oscillation</th>
<th>Conventional mechanical ventilation</th>
<th>Ratio of means (95% CI)</th>
<th>Weight (%)</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derdak 2002</td>
<td>53</td>
<td>54</td>
<td>25.0</td>
<td>0.99</td>
<td>(0.82 to 1.20)</td>
</tr>
<tr>
<td>Shah 2004</td>
<td>15</td>
<td>13</td>
<td>10.4</td>
<td>1.34</td>
<td>(0.91 to 1.97)</td>
</tr>
<tr>
<td>Bollen 2005</td>
<td>34</td>
<td>23</td>
<td>25.3</td>
<td>0.98</td>
<td>(0.81 to 1.19)</td>
</tr>
<tr>
<td>Mentzelopoulos 2007</td>
<td>27</td>
<td>27</td>
<td>28.2</td>
<td>1.38</td>
<td>(1.17 to 1.63)</td>
</tr>
<tr>
<td>Samransamrujkit 2005</td>
<td>7</td>
<td>9</td>
<td>11.0</td>
<td>1.26</td>
<td>(0.87 to 1.83)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>136</td>
<td>126</td>
<td><strong>100.0</strong></td>
<td><strong>1.16</strong></td>
<td>(0.97 to 1.37)</td>
</tr>
</tbody>
</table>

**Test for heterogeneity:** $t^2=0.02$, $\chi^2=10.50$, $df=4$, $P=0.03$, $I^2=62\%$

**Test for overall effect:** $z=1.67$, $P=0.10$

<table>
<thead>
<tr>
<th>Day 3</th>
<th>High frequency oscillation</th>
<th>Conventional mechanical ventilation</th>
<th>Ratio of means (95% CI)</th>
<th>Weight (%)</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derdak 2002</td>
<td>41</td>
<td>44</td>
<td>23.7</td>
<td>1.07</td>
<td>(0.88 to 1.30)</td>
</tr>
<tr>
<td>Shah 2004</td>
<td>11</td>
<td>10</td>
<td>15.0</td>
<td>1.21</td>
<td>(0.90 to 1.63)</td>
</tr>
<tr>
<td>Bollen 2005</td>
<td>30</td>
<td>23</td>
<td>24.6</td>
<td>1.00</td>
<td>(0.83 to 1.21)</td>
</tr>
<tr>
<td>Mentzelopoulos 2007</td>
<td>27</td>
<td>27</td>
<td>24.5</td>
<td>1.38</td>
<td>(1.14 to 1.67)</td>
</tr>
<tr>
<td>Samransamrujkit 2005</td>
<td>7</td>
<td>8</td>
<td>12.2</td>
<td>1.35</td>
<td>(0.96 to 1.90)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>116</td>
<td>112</td>
<td><strong>100.0</strong></td>
<td><strong>1.17</strong></td>
<td>(1.02 to 1.35)</td>
</tr>
</tbody>
</table>

**Test for heterogeneity:** $t^2=0.01$, $\chi^2=7.18$, $df=4$, $P=0.13$, $I^2=44\%$

**Test for overall effect:** $z=2.26$, $P=0.02$

Sud, BMJ 2010;340:c2327
HFOV Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>High frequency oscillation</th>
<th>Conventional mechanical ventilation</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 1994</td>
<td>10/29</td>
<td>12/29</td>
<td></td>
<td>13.0</td>
<td>0.83 (0.43 to 1.62)</td>
</tr>
<tr>
<td>Derdak 2002</td>
<td>28/75</td>
<td>38/73</td>
<td></td>
<td>42.6</td>
<td>0.72 (0.50 to 1.03)</td>
</tr>
<tr>
<td>Shah 2004</td>
<td>6/15</td>
<td>6/13</td>
<td></td>
<td>7.9</td>
<td>0.87 (0.37 to 20.4)</td>
</tr>
<tr>
<td>Bollen 2005</td>
<td>16/37</td>
<td>8/24</td>
<td></td>
<td>12.5</td>
<td>1.30 (0.66 to 2.55)</td>
</tr>
<tr>
<td>Mentzelopoulous 2007</td>
<td>11/27</td>
<td>18/27</td>
<td></td>
<td>20.6</td>
<td>0.61 (0.36 to 1.04)</td>
</tr>
<tr>
<td>Samransamruajkit 2005</td>
<td>2/6</td>
<td>5/10</td>
<td></td>
<td>3.4</td>
<td>0.67 (0.18 to 2.42)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>73/189</strong></td>
<td><strong>87/176</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>0.77 (0.61 to 0.98)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=3.36$, $df=5$, $P=0.64$, $I^2=0\%$

Test for overall effect: $z=2.12$, $P=0.03$

**Fig 2** | Hospital or 30 day mortality in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

HFOV in adults with ARDS is safe and may improve outcome – more study is needed

Sud, BMJ, 2010;340:c2327
OSCILLATE RCT

- CIHR/CCC Trials Group OSCILLATE trial
- Target sample size of 1200; 492 enrolled
- http://www.oscillatetrial.com/

The Oscillation for ARDS Treated Early (OSCILLATE) Trial

Co-Principal Investigators: Niall D. Ferguson, Maureen O. Meade

Steering Committee: ND Ferguson; MO Meade; DJ Cook; GH Guyatt; S Mehta; AS Slutsky; TE Stewart; SD Walter

In Collaboration with: The Canadian Critical Care Trials Group

Funded by: Canadian Institutes of Health Research, RCT Program
Randomized Trial

- OSCAR: High Frequency Oscillation in ARDS
- Target sample size of 802 (6/07 – 2/2012)
- Recruitment to date = 762
- Funding: NIHR Health Technology Assessment Programme – HTA (UK)

www.oscar-trial.org
Rescue Strategies in ARDS

HFOV as Rescue for Severe ARDS
Prone Positioning in adult patients with ARDS is associated with

A. Improved ventilation
B. Need for neuromuscular blockade
C. Increased complications
D. Reduced mortality in severe hypoxemia patients
Question 3

Prone Positioning in adult patients with ARDS is associated with

A. Improved ventilation
B. Need for neuromuscular blockade
C. Increased complications

D. Reduced mortality in severe hypoxemia patients
ARDS

- Bilateral patchy opacities
- “Baby Lung” Sitting on Top of a Consolidated Lung
- Posterior dependent lung consolidation
- Difficult to recruit
CT Imaging prior to Prone Position

Posterior Dependent Atelectasis and Edema
Prone Position effect on Oxygenation

**RR 1.23, CI 1.15 – 1.32**

<table>
<thead>
<tr>
<th>Study</th>
<th>Prone, N</th>
<th>Supine, N</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gattinoni et al²³</td>
<td>147</td>
<td>148</td>
<td>1.28 (1.15-1.42)</td>
</tr>
<tr>
<td>Watanabe et al²³</td>
<td>8</td>
<td>8</td>
<td>1.39 (1.16-1.66)</td>
</tr>
<tr>
<td>Curley et al²⁸</td>
<td>45</td>
<td>49</td>
<td>1.14 (0.95-1.37)</td>
</tr>
<tr>
<td>Papazian et al²⁹</td>
<td>13</td>
<td>13</td>
<td>1.64 (1.29-2.10)</td>
</tr>
<tr>
<td>Mancebo et al³¹</td>
<td>71</td>
<td>59</td>
<td>1.27 (1.09-1.49)</td>
</tr>
<tr>
<td>Chan et al³⁴</td>
<td>11</td>
<td>11</td>
<td>1.53 (1.00-2.33)</td>
</tr>
<tr>
<td>Demory et al³²</td>
<td>13</td>
<td>15</td>
<td>1.69 (1.28-2.24)</td>
</tr>
<tr>
<td>Ibrahim et al³³</td>
<td>11</td>
<td>11</td>
<td>1.30 (1.02-1.66)</td>
</tr>
<tr>
<td>Overall</td>
<td>319</td>
<td>314</td>
<td>1.34 (1.23-1.45)</td>
</tr>
<tr>
<td><strong>Overall effect</strong></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>²⁹%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gattinoni et al²³</td>
<td>121</td>
<td>139</td>
<td>1.25 (1.13-1.39)</td>
</tr>
<tr>
<td>Watanabe et al²⁵</td>
<td>8</td>
<td>8</td>
<td>1.38 (1.16-1.65)</td>
</tr>
<tr>
<td>Curley et al²⁸</td>
<td>41</td>
<td>47</td>
<td>1.19 (1.00-1.41)</td>
</tr>
<tr>
<td>Chan et al³⁴</td>
<td>8</td>
<td>7</td>
<td>2.09 (1.26-3.47)</td>
</tr>
<tr>
<td>Overall</td>
<td>178</td>
<td>201</td>
<td>1.30 (1.15-1.46)</td>
</tr>
<tr>
<td><strong>Overall effect</strong></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>³²%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gattinoni et al²³</td>
<td>95</td>
<td>132</td>
<td>1.20 (1.07-1.34)</td>
</tr>
<tr>
<td>Watanabe et al²⁵</td>
<td>8</td>
<td>8</td>
<td>1.46 (1.21-1.76)</td>
</tr>
<tr>
<td>Curley et al²⁸</td>
<td>29</td>
<td>41</td>
<td>1.16 (0.96-1.41)</td>
</tr>
<tr>
<td>Mancebo et al³¹</td>
<td>65</td>
<td>52</td>
<td>1.22 (1.06-1.40)</td>
</tr>
<tr>
<td>Chan et al³⁴</td>
<td>8</td>
<td>7</td>
<td>1.08 (0.66-1.77)</td>
</tr>
<tr>
<td>Overall</td>
<td>205</td>
<td>240</td>
<td>1.23 (1.15-1.32)</td>
</tr>
<tr>
<td><strong>Overall effect</strong></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>⁰%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In ARDS: RR 0.708, CI 0.503 – 0.997; p=0.048

Prone Position effect on Mortality

- Individual patient meta-analysis of the 4 major clinical trials
- Absolute mortality of severely hypoxemia ARDS patients is reduced by 10%

Rescue Strategies in ARDS

Prone Position as Rescue for Severe ARDS

Low Tidal Volume Ventilation

Increasing Severity of Lung Injury

Mild ARDS

Moderate ARDS

Severe ARDS

PaO$_2$/FiO$_2$
Prone Position Techniques

- Vollman Prone Positioner

- Rotoprone Therapy System (KCI, USA)
Prone Positioning
Univ. Michigan Prone Method

- 4 people
- 2 sheets
- Easy to do
- Easy to teach
- Quick
- Easy access to patient

With flat sheet, pull patient to one side of the bed.

Tuck flat sheet around patient arm in order to protect it and move patient.

Place a second flat sheet on the bed, tuck under patient. Everything will pull through when you turn the patient.

Carefully turn the patient over and position prone by pulling the sheet. This will allow the arm and sheet to pulled across the bed.

Discard the sheet that was pulled through, position lines and tubes.

Patient now prone. Place arms in swimmers position (one positioned up toward head, one at side. Place in Reverse Trendelenberg.)
To place supine reverse the process, place flat sheet over patient, tucking in one side under arm.

Place a second flat sheet on the bed, tuck under patient. Everything will pull through when you turn the patient.

Carefully turn the patient over and position prone by pulling the sheet. This will allow the arm and sheet to pull across the bed.

Discard the sheet that was pulled through, position lines and tubes, center patient in the bed.
Question 4

Which of the following is true regarding ECMO in adult patients with ARDS?

A. VA-ECMO is associated with decreased mortality compared to VV-ECMO
B. Anticoagulation is required but is not associated with increased complications
C. Transfer to a specialized center with ECMO capabilities is associated with decreased mortality
D. ECMO is contraindicated after ≥ 5 days of mechanical ventilation
Question 4

Which of the following is true regarding ECMO in adult patients with ARDS?

A. VA-ECMO is associated with decreased mortality compared to VV-ECMO

B. Anticoagulation is required but is not associated with increased complications

C. Transfer to a specialized center with ECMO capabilities is associated with decreased mortality

D. ECMO is contraindicated after ≥ 5 days of mechanical ventilation
**ECMO Inclusion Criteria**

- Belief that the disease is reversible
- Severe hypoxemia
- MV with high pressures < 7-10 days
- Failure of gas exchange
- Failed rescue strategies

**Exclusion Criteria**

- Irreversible pulmonary disease
- MV > 7-10 days on high pressures
- Contraindication to anticoagulation

---

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Mechanical Ventilation</td>
<td>There is no absolute contraindications to ECLS, as each patient is considered individually with respect to risks and benefits. There are conditions, however, that are known to be associated with a poor outcome despite ECLS, and can be considered as relative contraindications:</td>
</tr>
<tr>
<td>Pulmonary Compliance</td>
<td>Mechanical ventilation at high settings (FiO\textsubscript{2} &gt; 0.9, P-plat &gt; 30) for 7 days or more</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Major pharmacologic immunosuppression (absolute neutrophil count &lt; 400/mm3)</td>
</tr>
<tr>
<td>CNS hemorrhage that is recent or expanding</td>
<td>Contraindication to systemic anticoagulation</td>
</tr>
</tbody>
</table>
Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival, n (%)</td>
<td>19 (40)</td>
<td>153 (50)</td>
<td>268 (52)</td>
<td>301 (50)</td>
<td>0.22</td>
</tr>
<tr>
<td>Age (year), median (IQR)</td>
<td>25 (19, 35)</td>
<td>31 (21, 43)</td>
<td>36 (22, 49)</td>
<td>37 (23, 51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60 (56, 77)</td>
<td>61 (50, 75)</td>
<td>74 (60, 90)</td>
<td>75 (63, 90)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5 (56)</td>
<td>21 (55)</td>
<td>212 (50)</td>
<td>265 (44)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hours of ventilation, median (IQR)</td>
<td>72 (12, 192)</td>
<td>120 (33, 192)</td>
<td>55 (18, 143)</td>
<td>42 (17, 139)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac arrest, n (%)</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td>43 (8)</td>
<td>60 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Documented infections</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>150 (29)</td>
<td>210 (35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High frequency ventilation</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>16 (5)</td>
<td>50 (9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Inotropic agents/vasopressors</td>
<td>0 (0)</td>
<td>16 (5)</td>
<td>297 (57)</td>
<td>493 (82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>82 (16)</td>
<td>117 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>11 (2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>71 (14)</td>
<td>118 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neuromuscular blockade</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>242 (47)</td>
<td>338 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicarbonate infusion</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>110 (21)</td>
<td>137 (23)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- N = 1473 from ELSO, mean age 34 years
- 50% all-cause mortality
- ECMO mean duration 144 hours (~6 days)

Conventional Ventilation or ECMO for Severe Adult Respiratory Failure
UK Adult ECMO Study
CESAR. Peek and Firmin 2000-2006

180 ARDS Pts , 30 centers

Consent
Randomize

90 Conventional

90 Optimal+ECMO

47% Survival at 6 months
63% Survival

(68 ECMO)

766 patients screened, 180 randomized, and 68 patients (75%) actually received ECMO. Of patients assigned to consideration for treatment by ECMO, 63% (57/90) survived to 6 months without disability vs 47% (41/87) (relative risk, 0.69; 95% confidence interval [CI], 0.05 - 0.97; P = .03).

Exclusion criteria:
- high pressure (30cm PIP) or high FIO2 (0.8) for 7d, contraindication to heparin.
ECLS in ARDS
Prospective Randomized Trial, Cesar Trial, 2008

**Kaplan-Meier survival estimates, by allocation**

**31% Mortality reduction in Specialized Center**

ECMO 63% (57/90) survived to 6 months without disability vs. 47% (41/87)

Relative risk (death or severe disability), 0.69; 95% CI 0.05 – 0.97; \( P = .03 \); RR death 0.73; 95% CI 0.52-1.03
Meta-analysis of 3 ECMO RCTs

• Meta-analysis of the 3 RCTs found moderate, statistically significant heterogeneity in their reported risk ratios for mortality with and without ECMO (chi-square test $p = 0.09$, $I^2 = 58\%$).

• This means that differences in patient populations or methods between the studies affected the results (not unexpected considering the trials were published over a span of 30 yrs) and that a summary effect size derived from these published results may not reflect the true effect of ECMO on patient mortality.

• The summary risk ratio found by the meta-analysis was 0.93 (95% confidence interval, 0.71 to 1.22).

• **Conclusion:**
  
  • Thus, there is insufficient evidence to provide a recommendation for ECMO use among patients with respiratory failure resulting from influenza.

• However, clinicians should consider ECMO within the context of other salvage therapies for acute respiratory failure.

---

Meta-analysis of 3 ECMO RCTs

• **Conclusion:**
  • For clinicians at hospitals that do not have an ECMO program, it would be advisable:
  • to establish institutional guidelines to identify ECMO-eligible patients in a timely manner and
  • to establish a relationship with an ECMO-capable institution to facilitate safe inter-hospital transport of these potentially salvageable patients and
  • to be familiar with the general guidelines for extracorporeal life support cases and H1N1 cases in particular provided by the Extracorporeal Life Support Organization.

• **Future studies are needed to define the optimal use of this potentially life-saving intervention.**

Extracorporeal membrane oxygenation in pandemic flu: Insufficient evidence or worth the effort?*

- ECMO support is a reasonable therapy for patients who do not respond to conventional care
- Transfer these patients to an ECMO-capable ARDS referral center with special expertise
- Rescue therapies such as inhaled nitric oxide, prone positioning, high-frequency oscillatory ventilation, steroids in ARDS have no better proof that they are superior to conventional care in adults with ARDS, but clinicians often use them.
- All ECMO patients should be reported to ELSO
- > 40,000 patients currently in the ELSO registry

Clinical Findings and Demographic Factors Associated With ICU Admission in Utah Due to Novel 2009 Influenza A(H1N1) Infection

Russell R. Miller III, MD, MPH; Boaz A. Markewitz, MD, FCCP; Robert T. Rolfs, MD, MPH; Samuel M. Brown, MD; Kristin K. Dascomb, MD, PhD; Colin K. Grissom, MD, FCCP; Michael D. Friedrichs, MS; Jeanmarie Mayer, MD; Eliotte L. Hirshberg, MD; Jamie Conklin, MD; Robert Paine III, MD; and Nathan C. Dean, MD, FCCP

- 30 patients with H1N1-associated ARDS
- Median age 34
- Median P/F ratio 61 (52-100)
- Not treated with ECMO
- Mortality 26.6% (8/30)
- Deaths
  - 1 shock/hypoxemia
  - 3 severe hypoxic or anoxic brain injury
  - 1 strep sepsis
  - 1 support withdrawn

Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1)

- 2009-2010 H1N1-associated ARDS
- “ECMO-referred patients” 80, transferred to 4 adult ECMO centers in UK
- Matched with “Non-ECMO-referred patients” 1756), Swine Flu Triage Study
- Concurrent longitudinal cohort study
- Critically ill patients with H1N1 ARDS

80 referred for ECMO; 69 received (86.3%); hospital mortality 27.5%

**Table 2. Deaths Analyzed by Matching Methods**

<table>
<thead>
<tr>
<th>Matching method</th>
<th>ECMO-Refereed</th>
<th>Non-ECMO-Refereed</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propensity score</td>
<td>18/75 (24.0)</td>
<td>35/75 (46.7)</td>
<td>0.51 (0.31-0.84)</td>
<td>.008</td>
</tr>
<tr>
<td>GenMatch</td>
<td>18/75 (24.0)</td>
<td>38/75 (50.7)</td>
<td>0.47 (0.31-0.72)</td>
<td>.001</td>
</tr>
<tr>
<td>Individual</td>
<td>14/59 (23.7)</td>
<td>31/59 (52.5)</td>
<td>0.45 (0.26-0.79)</td>
<td>.006</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; RR, relative risk.

**EOLIA ECMO Trial**

- **ECMO** to rescue **Lung Injury** in severe **ARDS**
- Multicenter ECMO trial in adult severe ARDS
- Alain Combes MD, PI, France
- Control cohort with modern ARDS ventilator management, and rescue strategies allowed

**Inclusion criteria**
1. Severe ARDS defined according to usual criteria, and
2. Meeting 1 of the 3 following criteria of severity:
   a. \(\text{PaO}_2\text{FiO}_2\) ratio <50 mm Hg with FiO\(_2\) \(\geq\) 80% for >3 hours, despite optimization of mechanical ventilation and despite possible recourse to usual adjunctive therapies (NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion) OR
   b. \(\text{PaO}_2\text{FiO}_2\) ratio <80 mm Hg with FiO\(_2\) \(\geq\) 80% for >6 hours, despite optimization of mechanical ventilation and despite possible recourse to usual adjunctive therapies (NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion) OR
   c. pH <7.25 for >6 hours (RR increased to 35 min) resulting from MV settings adjusted to keep Pplat \(\leq\) 32 cm H\(_2\)O (first Vi reduction by steps of 1 mL/kg to 4 mL/kg then PEEP reduction to a minimum of 8 cm H\(_2\)O)
3. Obtain patient’s consent or emergency consent

**Randomization**

**Experimental Treatment Arm**
- Venovenous ECMO will be started as rapidly as possible
- Mechanical ventilation settings: volume-assist control mode, FiO\(_2\) 30–60%, PEEP \(\geq\) 10 cm H\(_2\)O, V-lowered to obtain a plateau pressure \(\leq\) 20 cm H\(_2\)O, RR 10–30 minute or APRV mode with high pressure level \(\leq\) 30 cm H\(_2\)O at low pressure level \(\geq\) 10 cm H\(_2\)O
- ECMO weaning according to protocol

**Control Conventional Treatment Arm**
- Conventional management of ARDS
- Ventilatory settings: volume-assist control mode, Vi 6 mL/kg of ideal body weight and PEEP adapted so as not to exceed plateau pressure of 25–30 cm H\(_2\)O
- In the case of refractory hypoxemia, the usual adjunctive therapeutics can be used: NO, prone position, HFO ventilation, almitrine infusion
- Cross over option to ECMO possible if refractory hypoxemia defined as SaO\(_2\) <80% for >6 hours, despite mandatory use of recruitment maneuvers, and inhaled NO/prostacyclin and if technically possible a test of prone position.

**Judgement criteria**

**Primary endpoint:** All-cause mortality at D60

**Secondary outcomes:**
- Mortality at D30 and D90, in the ICU and in-hospital
- Number of days, between inclusion and D60, alive without mechanical ventilation, without hemodynamic support and without organ failure
- Number of patients developing pneumothorax between D1 and D60
- Number of infectious, neurological and hemorrhagic complications
- Duration of mechanical ventilation, and ICU and hospital stays
CARDIOHELP System (Maquet)

- FDA approved 4-26-2011: market in US as cardiac/respiratory assist device for up to 6 hours, and for ground/air transportation
- HLS Advanced Tubing and Priming Set (2 sets: 7.0 and 5.0)
- Light and compact, touchscreen
- Disposables, integrated sensors (Hb, saO2, sVO2, temperature)
- VV-ECMO or VA-ECMO
Rescue Strategies in ARDS

ECMO as Rescue for Severe ARDS

Increasing Intensity of Intervention

Low – Moderate PEEP
NIV
Higher PEEP

Low Tidal Volume Ventilation
Increasing Severity of Lung Injury

Mild ARDS
Moderate ARDS
Severe ARDS

PaO₂/FiO₂
Novalung Active

Heparin-coated PMP Hollow fiber membrane, Centrifugal pump
Question 5

What is the optimal timing for tracheostomy in patients with acute respiratory failure?

A. 1-4 days after intubation
B. 4-6 days after intubation
C. 6-8 days after intubation
D. ≥ 10 days after intubation
Question 5

What is the optimal timing for tracheostomy in patients with acute respiratory failure?

A. 1-4 days after intubation
B. 4-6 days after intubation
C. 6-8 days after intubation
D. ≥ 10 days after intubation
Tracheostomy vs. Prolonged Intubation

A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients* 

Mark J. Rumbak, MD; Michael Newton, MD; Thomas Truncale, DO; Skai W. Schwartz, PhD; James W Adams, MD; Patrick B. Hazard, MD

- Adult pts projected to need MV for 14 days
- N = 120
- Early tracheostomy – within 48 hrs
- Late tracheostomy – within 14-16 days

Crit Care Med 2004 Vol. 32, No. 8:1689
Survival post-intubation

Kaplan-Meier curve. The time to death is displayed. There is a significantly better mortality rate in the early tracheotomy group than the prolonged translaryngeal group at 30 days ($p < 0.005$).

Mortality 31.7% vs. 61.7%
<table>
<thead>
<tr>
<th>Outcome Measurement</th>
<th>Early Tracheotomy (n = 60)</th>
<th>Prolonged Translaryngeal Intubation (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died (%)</td>
<td>19 (31.7)</td>
<td>37 (61.7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>3 (5)</td>
<td>15 (25)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Days in ICU ± SD</td>
<td>4.8 ± 1.4</td>
<td>16.2 ± 3.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Days mechanically ventilated ± SD</td>
<td>7.6 ± 4.0</td>
<td>17.4 ± 5.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Days sedated ± SD</td>
<td>3.2 ± 0.4</td>
<td>14.1 ± 2.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Days on high-dose pressors</td>
<td>3.5 ± 4</td>
<td>3.0 ± 4.5</td>
</tr>
<tr>
<td>Organism(s) causing pneumonia: Methicillin-resistant <em>Staphylococcus aureus, Pseudomonas aeruginosa</em> mixture</td>
<td>1, 1, 1</td>
<td>5, 5, 5</td>
</tr>
</tbody>
</table>

<sup>a</sup><sub>p < .005; b p < .001</sub>. There was a significant difference between the early tracheotomy groups and the prolonged translaryngeal intubation group in outcome measures. Some patients were sent to a step-down while still on mechanical ventilation.
Early tracheotomy in critically ill medical patients who undergo \( \geq 14 \) days of ventilation may have significant benefits over delayed tracheotomy.
RCT, n = 209
- Early trach, 145 (6-8 days)
- Late trach, 119 (13-15 days)

12 Italian ICUs, 6/2004-2008

Primary endpoint was VAP
- 30 (14%) Early trach
- 44 (21%) Late trach
- P = 0.07 (VAP defined by CPIS)
Early = 1-4 days after intubation
Late = ≥ 10 days after intubation

Survival at 30 days

Proportion surviving

Time from randomisation (days)

Number at risk

Early 451 417 381 352 341 321 315
Late 448 426 381 351 328 320 309

Treatment group: Early Late

n = 909
TracMan Trial, Largest trial, n=909, UK

- No difference in VAP rates, ventdays, mortality
- Significantly decreased sedation use – early trach
Patient

- A 65 yo female underwent elective pulmonary lobectomy (RLL) for lung cancer.
- She has a prior 52-pack-year hx of smoking and PMH of chronic obstructive pulmonary disease (COPD).
- She requires mechanical ventilation postoperatively and the RT recognizes that there is significant auto-PEEP present and notifies you.
Question 6

Which of the following methods would be most reliable in reducing auto-PEEP?

A. Decrease exogenous positive-end-expiratory pressure (PEEP)
B. Increase inspiratory time
C. Increase expiratory time
D. Decrease expiratory time
Question 6

Which of the following methods would be most reliable in reducing auto-PEEP?

A. Decrease exogenous positive-end-expiratory pressure (PEEP)
B. Increase inspiratory time
C. Increase expiratory time
D. Decrease expiratory time

**C. Increase expiratory time**
Auto-PEEP
Auto-PEEP & VT

Effect of Lengthening Expiratory time during PCV
Estimating auto-positive end-expiratory pressure (auto-PEEP)

**FIGURE 2.** Expiratory hold techniques to estimate auto-PEEP. The exhalation valve is closed during an expiratory hold at the end of the set expiratory time. When the flow equals zero, airway pressure rises to the auto-PEEP level. With the valve open, flow continues, and the additional exhaled volume equals the volume of trapped gas.
Question 7

Regarding Sedation and Delirium in the ICU:

A. Reintubation rates are higher when spontaneous breathing trials are paired with sedation holidays

B. Dexmedetomidine is associated with higher costs than lorazepam

C. After adjusting for patient age and severity of illness, use of lorazepam no longer correlates with the development of delirium

D. ICU delirium affects long term outcomes following hospital discharge
A. Reintubation rates are higher when spontaneous breathing trials are paired with sedation holidays

B. Dexmedetomidine is associated with higher costs than lorazepam

C. After adjusting for patient age and severity of illness, use of lorazepam no longer correlates with the development of delirium

D. ICU delirium affects long term outcomes following hospital discharge
Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

- Paired daily awakening trial and spontaneous breathing trial
- Increased days breathing without assistance and earlier ICU discharge, approx 4 days
- Lower mortality during the year after enrollment
  
  HR 0.68 95% CI 0.50 – 0.92
  NTT 7.4

Wake up and Breathe!
Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit

ICU Delirium Affects Mortality at 6 months

Ely JAMA 2004;291:1753-1762
Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients


- Lorazepam use, Severity of illness and Age
- Independent risk factors for transitioning to ICU delirium

Choice of sedation is a modifiable risk factor for delirium
Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients
The MENDS Randomized Controlled Trial

- 106 patients
- Randomized, double blind trial
- Similar costs between arms
- More days alive without delirium or coma
- More days at targeted level of sedation

Pandharipande, JAMA 2007; 298 (22)