ARDS:
A CASE-BASED REVIEW AND UPDATE

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Objectives

This session is intended to provide a case-based review of the following concepts and ARDS-related learning outcomes:

- Case definition(s), epidemiology & etio-pathogenesis.

- Clinical presentation, diagnosis & differential diagnoses

- Contemporary concepts, clinical decision-making as well as practically-relevant issues in ARDS management.
Case #1

- A 70-year-old man was admitted to the CT-ICU
  - acute hypoxemic respiratory failure
- 48 hours earlier
  - He underwent a surgical resection of the left lower lobe for stage IIIB adenocarcinoma of the lung.
- Intra-operative course
  - He received a total fluid infusion of 5.5 L (including 3 units of packed red blood cells)
  - The cumulative fluid infusion given during the peri-operative period was 8.0 L with a net negative 0.7 L
Case#1

- Post Operative course
  - Extubated and transferred to the ward
  - 24 hours later
    - Significant dyspnea and hypoxemia were noted
    - re-intubated
Case#1

- **Past Medical History**
  - Adenocarcinoma of the lung, stage IIIb, diagnosed 3 months before surgery, treated with preoperative neo-adjuvant chemotherapy and radiotherapy
  - History of moderate COPD

- **Social History**
  - 80-pack-years of cigarette smoking, chronic alcohol consumption of 2-4 beers a day.

- **Pre-operative evaluation**
  - Complete blood count and blood chemistry were normal
  - Pre-operative evaluation for chronic heart disease was negative
  - Forced Expiratory Volume in 1s (FEV1) was 1.79 L; 58% of the predicted value; calculated post-operative FEV1 was 49% of the predicted value
ICU Admission

- **Physical examination**
  - *Vital signs & Cardio-Respiratory*
    - BP 100/70 mmHg, Pulse 120/min, Respirations 36/min, SpO2 of 85% on 100% Non rebreather, Temperature 37.0°C
    - S1, S2 normal
    - Decreased breath sounds over the left lower lung field, diffuse end-inspiratory crackles over the remaining lobes.

- **Laboratory Data**
  - *Normal complete blood count and chemistry*
  - *Blood cultures, done*
At this point

Q1: Does this patient have no-ARDS, mild ARDS, moderate ARDS or severe ARDS?

Q2: What is the likely etio-pathogenesis?

Q3: What is the expected outcome?
Arterial blood gases:

\[
\text{PaO}_2 \geq 300\text{mmHg}
\]

\[
\text{FiO}_2 \ 0.6, \\
\text{PaO}_2 \ 70\text{mmHg}, \\
\text{PaCO}_2 \ 45\text{mmHg}, \\
\text{PaO}_2/\text{FiO}_2 \ 117
\]

\[
\text{PaO}_2 \leq \text{FiO}_2
\]
Imaging...
Volume status/cardiac filling pressure estimation

- Clinical exam + EMR section labeled I/O/NB

- Transthoracic echocardiography:
  - Ejection fraction 60 %, normal left ventricular systolic function. Mild right ventricular dilation

- Right heart catheterization:
  - Cardiac Output (CO): 7.74 L/min (normal 5-7 L/min)  
    Cardiac Index (CI): 4.8 L/min/m² (normal 3-5 L/min/m²)  
    CVP: 8 mmHg  
    SVRI: 960 dynes/sec/cm⁵/m² (normal 1200-1800)  
    Pulmonary artery systolic pressure (PASP): 59 mmHg  
    Pulmonary Wedge Pressure: 11 mmHg
**Definition**

1967: Ashbaugh et al. described a condition in adults which was similar to the respiratory distress syndrome of infants

1971: The term ARDS was coined by Petty & Ashbaugh for this condition and diagnostic criteria were outlined, the 'Petty Diagnostic Criteria'

<table>
<thead>
<tr>
<th>1. clinical setting:</th>
<th>2. CXR:</th>
<th>3. physiology:</th>
<th>4. pathology:</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. catastrophic event - pulmonary - non-pulmonary</td>
<td>• diffuse pulmonary infiltrates</td>
<td>i. PaO2 50 mmHg with a FIO2 ≥ 0.6</td>
<td>i. heavy lungs - usually 1000 g</td>
</tr>
<tr>
<td>ii. exclusions - chronic respiratory disease - LV dysfunction</td>
<td>i. interstitial – early</td>
<td>ii. CT 50 ml/cmH2O - usually 20-30 ml/cmH2O</td>
<td>ii. congestive atelectasis</td>
</tr>
<tr>
<td>iii. respiratory distress - RR &gt; 20 bpm - laboured breathing</td>
<td>ii. alveolar - late</td>
<td>iii. QS/QT increased</td>
<td>iii. hyaline membranes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>iv. VD/VT increased, increased V/Q anomaly</td>
<td>iv. fibrosis</td>
</tr>
</tbody>
</table>
The American-European Consensus Conference Definition of Acute Lung Injury and ARDS, AECC

<table>
<thead>
<tr>
<th></th>
<th>Timing</th>
<th>Oxygenation (PaO$_2$/FiO$_2$)</th>
<th>Chest Radiograph</th>
<th>Pulmonary Artery Wedge pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>Acute onset</td>
<td>≤ 300 mmHg (40 kPa) (regardless of PEEP)</td>
<td>Bilateral infiltrates</td>
<td>≤18 mmHg/no evidence of left atrial hypertension</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute onset</td>
<td>≤ 200 mmHg (26 kPa) regardless of PEEP</td>
<td>Bilateral infiltrates</td>
<td>≤ 18 mmHg or no evidence of left atrial hypertension</td>
</tr>
</tbody>
</table>
## Table 1. The AECC Definition—Limitations and Methods to Address These in the Berlin Definition

<table>
<thead>
<tr>
<th>AECC Definition</th>
<th>AECC Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Acute onset</td>
</tr>
<tr>
<td><strong>ALI category</strong></td>
<td>All patients with PaO(_2)/FiO(_2) &lt; 300 mm Hg</td>
</tr>
<tr>
<td><strong>Oxygenation</strong></td>
<td>PaO(_2)/FiO(_2) &lt; 300 mm Hg (regardless of PEEP)</td>
</tr>
<tr>
<td><strong>Chest radiograph</strong></td>
<td>Bilateral infiltrates observed on frontal chest radiograph</td>
</tr>
<tr>
<td><strong>PAWP</strong></td>
<td>PAWP ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension</td>
</tr>
<tr>
<td><strong>Risk factor</strong></td>
<td>None</td>
</tr>
</tbody>
</table>

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[^4]: AECC Criticism
AECC Criticism, Hypoxemia

Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome

- 48 patients with ARDS diagnosis by AECC criteria with PEEP = 0 cm H₂O
- After 6 hrs of PEEP (mean 11.5 cm H₂O) 52% had P/F > 200 mm Hg
- After 24 hrs of PEEP (mean 12.8 cm H₂O) 62% had P/F > 200 mm Hg
- Mortality 61% vs 53%
AECC Criticism, CXR

Interobserver Variation in Interpreting Chest Radiographs for the Diagnosis of Acute Respiratory Distress Syndrome

MAURICE O. MEADE, RICHARD J. COOK, GORDON H. GAYATT, RYAN GROLL, JOHN R. KACHURA, MICHEL BEMARD, DEBORAH J. COOK, ARTHUR S. SLUTSKY, and THOMAS E. STEWART

To measure the reliability of chest radiographic diagnosis of acute respiratory distress syndrome (ARDS) we conducted an observer agreement study in which two of eight intensivists and a radiologist, blinded to one another’s interpretation, reviewed 778 radiographs from 99 critically ill patients. One intensivist and a radiologist participated in pilot training. Raters made a global rating of the presence of ARDS on the basis of diffuse bilateral infiltrates. We assessed interobserver agreement in a pairwise fashion. For raters pairings in which one rater had not participated in the consensus process we found moderate levels of rater (0.68 to 0.80), chance-corrected (κ = 0.38 to 0.55), and chance-independent (κ = 0.53 to 0.75) agreement. The pair of raters who participated in consensus training achieved excellent to almost perfect raw (0.88 to 0.94), chance-corrected (κ = 0.72 to 0.80), and chance-independent (κ = 0.74 to 0.89) agreement. We conclude that intensivists without formal consensus training can achieve moderate levels of agreement. Consensus training is necessary to achieve the substantial or almost perfect levels of agreement optimal for the conduct of clinical trials. Meade MO, Cook RJ, Gayatt DH, Groll R, Kachura JR, Bemard M, Cook DJ, Slutsky AS, Stewart TE. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome.
Acute Respiratory Distress Syndrome
The Berlin Definition

Table 1. The AECC Definition—Limitations and Methods to Address These in the Berlin Definition

<table>
<thead>
<tr>
<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 acute⁴</td>
</tr>
<tr>
<td>ALI category</td>
<td>All patients with ( \text{PaO}_{2}/\text{FiO}_2 &lt; 300 \text{ mm Hg} )</td>
<td>Misinterpreted as ( \text{PaO}_{2}/\text{FiO}_2 = 201-300 ), leading to confusing ALI/ARDS term</td>
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<td></td>
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<tr>
<td>Oxygenation</td>
<td>( \text{PaO}_{2}/\text{FiO}_2 \leq 300 \text{ 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 )⁷-⁸</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Chest radiograph</td>
<td>Bilateral infiltrates observed on frontal chest radiograph</td>
<td>Poor interobserver reliability of chest radiograph interpretation⁸⁹</td>
</tr>
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<td></td>
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<tr>
<td>PAWP</td>
<td>PAWP ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension</td>
<td>High PAWP and ARDS may coexist¹⁰¹¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor interobserver reliability of PAWP and clinical assessments of left atrial hypertension¹²</td>
</tr>
<tr>
<td>Risk factor</td>
<td>None</td>
<td>Not formally included in definition⁴</td>
</tr>
</tbody>
</table>
### Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Acute Respiratory Distress Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Within 1 week of a known clinical insult or new or worsening respiratory symptoms</td>
</tr>
<tr>
<td><strong>Chest imaging</strong></td>
<td>Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules</td>
</tr>
<tr>
<td><strong>Origin of edema</strong></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><strong>Oxygenation</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>$200 \text{ mm Hg} &lt; \frac{\text{Pao}_2}{\text{FiO}_2} \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}$</td>
</tr>
<tr>
<td>Moderate</td>
<td>$100 \text{ mm Hg} &lt; \frac{\text{Pao}_2}{\text{FiO}_2} \leq 200 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$</td>
</tr>
<tr>
<td>Severe</td>
<td>$\frac{\text{Pao}_2}{\text{FiO}_2} \leq 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$</td>
</tr>
</tbody>
</table>

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: \([\text{Paco}_2/\text{FiO}_2 \times \text{ (barometric pressure/760)}]\).

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


- Severe Sepsis: 26%
- Pneumonia: 35%
- Aspiration: 15%
- Trauma: 11%
- Other: 13%

DDX:
- Left ventricular failure/volume overload
- Mitral stenosis
- Pulmonary veno-occlusive disease
- Lymphangitic spread of malignancy
- Interstitial and/or airway disease
- Hypersensitivity pneumonia
- Acute eosinophilic pneumonia
- Acute interstitial pneumonitis

Other:
- Massive transfusion, DIC (22.2%), drowning, pancreatitis, reperfusion, salicylate and narcotic OD, fat/amniotic embolism, smoke/chemical inhalation. **High FiO2 (+/- ?)**
Pathological Stages

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial, &quot;exudative&quot;</td>
<td>&quot;Proliferative&quot; stage-</td>
<td>Some patients progress to a third &quot;fibrotic&quot; stage, characterized by obliteration of normal lung architecture, diffuse fibrosis, and cyst formation</td>
</tr>
<tr>
<td></td>
<td>stage-diffuse alveolar</td>
<td>resolution of pulmonary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>damage within the first</td>
<td>edema, proliferation of</td>
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<tr>
<td></td>
<td>week</td>
<td>type II alveolar cells,</td>
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<td></td>
<td></td>
<td>squamous metaplasia,</td>
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<td></td>
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<td>interstitial infiltration</td>
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<td></td>
<td></td>
<td>by myofibroblasts, and</td>
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<td>early deposition of</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>collagen.</td>
<td></td>
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</tbody>
</table>
Pathophysiology
CORE MANAGEMENT OF ARDS
(“ARDS ALWAYS EVENTS” “ARDS BUNDLE”)

The 1, 2 & 3 of ARDS mgt.
I. Mechanical Ventilatory Strategy
ARDS
Mechanical Ventilation

- Ventilator associated lung injury
  - Volutrauma
  - Atelectotrauma
  - Biotrauma
  - Barotrauma
  - Air embolism/translocation
NHLBI ARDS Network

- Compared low tidal volumes (6ml/kg of ideal body weight) against conventional tidal volumes (12ml/kg ideal body weight)
  - Significant decrease in mortality associated with the use of low tidal volumes (39.8% versus 31%, $P=0.007$)
NHLBI ARDS Network
Main Outcome Variables

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Low Vt</th>
<th>Traditional Vt</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge home and breathing without assistance (%)</td>
<td>31.0</td>
<td>39.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Breathing without assistance by day 28 (%)</td>
<td>65.7</td>
<td>55.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of ventilator-free days, days 1 to 28</td>
<td>12 ± 11</td>
<td>10 ± 11</td>
<td>0.007</td>
</tr>
<tr>
<td>Barotrauma, days 1 to 28 (%)</td>
<td>10</td>
<td>11</td>
<td>0.43</td>
</tr>
<tr>
<td>No. of days without failure of nonpulmonary organs or systems, days 1 to 28</td>
<td>15 ± 11</td>
<td>12 ± 11</td>
<td>0.006</td>
</tr>
</tbody>
</table>
NHLBI ARDS Network
Main Organ Failure Free Days

Median Organ Failure Free Days

- Pulmonary
- CNS
- Hepatic
- Cardiovascular
- Coagulation
- Renal

Purple bar: = 6 ml/kg
Yellow bar: = 12 ml/kg
Vent settings to improve oxygenation

PEEP and FiO₂ are adjusted in tandem

- **PEEP**
  - Increases FRC
    - Prevents progressive atelectasis and intrapulmonary shunting
    - Prevents repetitive opening/closing (injury)
  - Recruits collapsed alveoli and improves V/Q matching
    - Resolves intrapulmonary shunting
    - Improves compliance
  - Enables maintenance of adequate PₐO₂ at a safe FiO₂ level
- **Disadvantages**
  - Increases intrathoracic pressure (may require pulmonary a. catheter)
  - May lead to ARDS
  - Rupture: PTX, pulmonary edema

Oxygen delivery (DO₂), not PaO₂, should be used to assess optimal PEEP.
Inclusion Criteria: Acute onset of
1. $\text{Pao}_2/\text{FiO}_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

Part I: Ventilator Setup and Adjustment
1. Calculate predicted body weight (PBW)
   - Males = $50 + 2.3 \times \text{[height (inches)]} - 60$
   - Females = $45.5 + 2.3 \times \text{[height (inches)]} - 60$
2. Select any ventilator mode
3. Set ventilator settings to achieve initial $V_t = 8 \text{ ml/kg PBW}$
4. Reduce $V_t$ by 1 ml/kg at intervals $\leq 2$ hours until $V_t = 6 \text{ ml/kg PBW}$
5. Set initial rate to approximate baseline minute ventilation (not $>35$ bpm)
6. Adjust $V_t$ and RR to achieve pH and plateau pressure goals below.

Oxygenation Goal: $\text{PaO}_2 \geq 55-80$ mmHg or $\text{SpO}_2 \geq 88-95$
Use a minimum PEEP of 5 cm H$_2$O. Consider use of incremental $\text{FiO}_2$/PEEP combinations such as shown below (not required) to achieve goal.

| Lower PEEP/higher $\text{FiO}_2$ |
|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| $\text{FiO}_2$      | 0.3    | 0.4    | 0.4    | 0.5    | 0.5    | 0.6    | 0.7    | 0.7    |
| PEEP                | 5      | 5      | 8      | 8      | 10     | 10     | 10     | 12     |
| $\text{FiO}_2$      | 0.7    | 0.8    | 0.9    | 0.9    | 0.9    | 1.0    |        |        |
| PEEP                | 14     | 14     | 14     | 16     | 18     | 18-24  |        |        |

| Higher PEEP/lower $\text{FiO}_2$ |
|----------------------|--------|--------|--------|--------|--------|--------|--------|
| $\text{FiO}_2$      | 0.3    | 0.3    | 0.3    | 0.3    | 0.3    | 0.4    | 0.4    | 0.5    |
| PEEP                | 5      | 8      | 10     | 10     | 14     | 14     | 16     | 16     |
| $\text{FiO}_2$      | 0.5    | 0.5-0.8| 0.8    | 0.9    | 1.0    | 1.0    |        |        |
| PEEP                | 18     | 20     | 22     | 22     | 22     | 24     |        |        |

Plateau Pressure Goal: $\leq 30$ cm H$_2$O
Check $P_{plat}$ (0.5 second Inspiratory pause), at least q4h and after each change in PEEP or $V_t$.
If $P_{plat} > 30$ cm H$_2$O: decrease $V_t$ by 1 ml/kg steps (minimum = 4 ml/kg).
If $P_{plat} < 25$ cm H$_2$O and $V_t < 6$ ml/kg, increase $V_t$ by 1 ml/kg until $P_{plat} > 25$ cm H$_2$O or $V_t = 6$ ml/kg.
If $P_{plat} < 30$ and breath stacking or dysynchrony occurs: may increase $V_t$ in 1 ml/kg increments to 7 or 8 ml/kg if $P_{plat}$ remains $\leq 30$ cm H$_2$O.
ARDS
Mechanical Ventilation

![Graph showing P_\text{peak}, P_\text{init}, and P_\text{plat}](graph.png)
ARDS
Mechanical Ventilation

■ Plateau pressure (measured during an inspiratory hold of 0.5 sec) less than 30 cm H₂O,
  - High plateau pressures vastly elevate the risk for harmful alveolar distension (volutrauma).

■ If plateau pressures remain elevated after following the above protocol, further strategies should be tried:
  - Reduce tidal volume, to as low as 4 mL/kg by 1 mL/kg stepwise increments.
  - Sedate the patient to minimize ventilator-patient dyssynchrony.
  - Consider other mechanisms for the increased plateau pressure
ARDS
High versus Low PEEP

Higher PEEP along with low tidal volume ventilation should be considered for patients receiving mechanical ventilation for ARDS. This suggestion is based on a 2010 meta-analysis of 3 randomized trials (n=2,229) testing higher vs. lower PEEP in patients with acute lung injury or ARDS, in which ARDS patients receiving higher PEEP had a strong trend toward improved survival.
ARDS
High versus Low PEEP

- However, patients with milder acute lung injury (paO2/FiO2 ratio > 200) receiving higher PEEP had a strong trend toward harm in that same meta-analysis.

- Higher PEEP can conceivably cause ventilator-induced lung injury by increasing plateau pressures, or cause pneumothorax or decreased cardiac output. These adverse effects were not noted in the largest ARDSNet trial (2004) testing high vs. low PEEP.
Potential benefits of hypercapnia in patients with ARDS

- Decrease in TNF-alpha release by alveolar macrophages
- Decrease in PMNL-endothelial cell adhesion
- Decrease in Xanthine oxidase activity
- Decrease in NOS activity
- Reduction of IL-8
Potential harms of hypercapnia in patients with CVT-ARDS
ARDS

Mechanical Ventilation

**pH GOAL: 7.30-7.45**

**Acidosis Management:** (pH < 7.30)
- If pH 7.15-7.30: Increase RR until pH > 7.30 or PaCO₂ < 25 (Maximum set RR = 35).

**If pH < 7.15:** Increase RR to 35.
- If pH remains < 7.15, V̇: may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).
- May give NaHCO₃

**Alkalosis Management:** (pH > 7.45)
- Decrease rate if possible.

**I:E RATIO GOAL:** Recommend that duration of inspiration be ≤ duration of expiration.

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**PART II: WEANING**

A. Conduct a **SPONTANEOUS BREATHING TRIAL** daily when:
1. FiO₂ ≤ 60% and PEEP ≤ 8.
2. PEEP and FiO₂ ≤ values of previous day.
3. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 30% for 5 minutes to detect effort.)
4. Systolic BP ≥ 90 mmHg without vasopressor support.
5. No neuromuscular blocking agents or blockade.

If all above criteria are met and subject has been in the study for at least 12 hours, initiate a trial of UP TO 120 minutes of spontaneous breathing with FiO₂ ≤ 0.5 and PEEP ≤ 5:
1. Place on T-piece, trach collar, or CPAP ≤ 5 cm H₂O with PS ≤ 5
2. Assess for tolerance as below for up to two hours.
   - SpO₂ ≥ 90: and/or PaO₂ ≥ 60 mmHg
   - Spontaneous V̇: ≥ 4 ml/kg PBW
   - RR ≤ 35/min
   - pH ≥ 7.3
   - No respiratory distress (distress = 2 or more)
     - HR > 120% of baseline
     - Marked accessory muscle use
     - Abdominal paradox
     - Diaphoresis
     - Marked dyspnea
3. If tolerated for at least 30 minutes, consider extubation.
4. If not tolerated, resume pre-weaning settings.

---

**Definition of UNASSISTED BREATHING**
(Different from the spontaneous breathing criteria as PS is not allowed)

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP less than or equal to 5 cm H₂O without pressure support or IMV assistance.
II. Cardiovascular Management
Vent settings to improve oxygenation

Oxygen delivery ($DO_2$), not $PaO_2$, should be used to assess optimal PEEP.
Fluid management and vasoactive support

- **FACTT trial**
  - *Prospective, Randomized, Multi-Center Trial*
  - *Utility and safety of using a pulmonary artery catheter versus central venous catheter to guide the volume replacement*
  - *Liberal versus conservative fluid replacement*
Patients were treated with the specific fluid management strategy (to which they were randomized) for 7 days or until unassisted ventilation, whichever occurs first.

The study enrolled 1000 patients and showed no benefit with PAC guided fluid therapy over the less invasive CVC guided therapy.
The Use of Conservative fluid management strategy was associated with:

- Significant improvement in oxygenation index
- Significant improvement in Lung Injury score
- Increase in the number of ventilator-free days
III. Generic Supportive Care
Supportive Therapies

- Treat underlying infection
- DVT prophylaxis / stress ulcer prevention
- HOB 30°
- Hand washing
- Use full barriers with chlorhexidine
- Sedation / analgesia
- Feeding protocol
- Avoid contrast nephropathy
- Pressure ulcer prevention, turn Q2h
MANAGEMENT OF REFRACTORY ARDS

THE PTS WITH ARDS
ARDS+ Case Study - Admission

- 46 yo unrestrained female MVA
- Fractures
  - Rt radial, ulna, fibula
  - Lt ankle
- RML contusion
- CT head and c-spine negative
- Pt c/o left chest pain and sedated with morphine and diprivan
- VSS
- Admission day CXR as shown
Case Study - Day 2

- Pt transported to OR for fx repair - VSS

- 24 hours later pt developed respiratory distress

- Decision made to initiate oxygen supplementation using a NRB mask, & a CXR & ABG requested/obtained [in addition to a cluster of indicated/Semi-indicated and NOT-indicated diagnostic evaluations].

- CXR revealed diffuse patchy infiltrates, essentially a worse version of the previous days CXR
Case Study

- Pt placed on 1.0 mask BiPAP 15/10
- Pt increasingly agitated, ↑ SOB, use of accessory muscles
- Pt subsequently intubated
  - 1.0/AC/550/14/8
  - SaO2 @ 30minutes - 78%; ABG pending; Post intubation CXR pending?
- Pt sedated
- PEEP ↑12, then 14 cmH₂O
<table>
<thead>
<tr>
<th>Date</th>
<th>4/17</th>
<th>4/19</th>
<th>4/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>0233</td>
<td>1000</td>
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</tr>
<tr>
<td>FiO₂</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>NRB</td>
<td>NRB</td>
<td>A/C</td>
</tr>
<tr>
<td>Rate</td>
<td>14</td>
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</tr>
<tr>
<td>Volume</td>
<td>550</td>
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<td>MAP</td>
<td></td>
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</tr>
<tr>
<td>AMP</td>
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<td></td>
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<tr>
<td>PIP</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PEEP</td>
<td></td>
<td>10</td>
<td></td>
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<tr>
<td>pH</td>
<td>7.38</td>
<td>7.38</td>
<td>7.27</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>36</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>PaO₂</td>
<td>68</td>
<td>49</td>
<td>80</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>21</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>SaO₂</td>
<td>92</td>
<td>82</td>
<td>93</td>
</tr>
<tr>
<td>TcCO₂</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case Study

- CXR - 4/21 - 01:00 hrs
- Although ABG’s improved, pt became increasingly agitated
  - RR ↑ 30’s
  - High pressure limit
  - BP, HR ↑
  - SaO2 ↓ 40’s
WHERE DO WE GO FROM HERE?
ARDS+

- NMB (Paralysis)
- Inhaled NO
- Steroids
- Prone Position
- High Frequency Oscillatory Ventilation
- ECMO
Neuromuscular Blockade
- Neuromuscular blockers in early acute respiratory distress syndrome.
  

  - This multicenter RCT of 340 patients with severe ARDS found early use of 48 hours of neuromuscular blockade reduced mortality compared to placebo (NNT of 11 to prevent one death at 90 days in all patients, and a NNT of 7 in a prespecified analysis of patients with a PaO2:FiO2 less than 120).
Neuromuscular blockers in early acute respiratory distress syndrome.


- Lowest dose
- Shortest duration
- Not with steroids if possible
Inhaled Nitric Oxide
Inhaled Nitric Oxide
Inhaled Nitric Oxide

Bronchial and vascular smooth muscle dilator.

Decreased platelet Adherence and Aggregation

Improved Ventilation - Perfusion matching

Reduction in Pulmonary Artery Pressure and pulmonary Vascular Resistance
Two Prospective, Randomized, Placebo Controlled Clinical Trials to date

Failed to demonstrate an improvement in the survival.

However, there was improvement in the oxygenation...
Steroids?
Steroids?

1. Don`t do it.

2. Okay.........avoid if possible

3. If doing it, do it right.
Corticosteroid Therapy in ARDS: Better late than never?

High-dose corticosteroids in early ARDS
- Do not lessen the incidence of ARDS among patients at high risk
- Do not reverse lung injury in patients with early ARDS/worse recovery
- Have no effect on mortality/even increase mortality rate
- Significantly increase the incidence of infectious complications

High-dose corticosteroids for unresolving ARDS of ≥ 7 days duration who do not have uncontrolled infection
- There are several challenges associated with the interpretation of this trial. A large clinical trial is needed to clearly demonstrate a survival advantage that outweighs the potential risks.
- Patient selection: Lack of clinical improvement rather than use of only the LIS
- Aggressive search for and treatment of infectious complications is necessary.
- Several questions remain: Timing, dosage, and duration of late steroid therapy in ARDS/Appropriate time window for corticosteroid administration, between early acute injury and established postaggressive fibrosis.
Steroids?


Steroids?

- A protocol for steroids in late ARDS, based on the Meduri paper*
- The patient must have no demonstrable infection
  - *broncho-alveolar lavage may be necessary to confirm this.* This includes undrained abscesses, disseminated fungal infection and septic shock
- Steroids should not be started less than 7 days, or more than 28 days, from admission
- The patient should not have a history of gastric ulceration of active gastrointestinal bleeding
- Patients with burns requiring skin grafting, pregnant patients, AIDS, and those in whom life support is expected to be withdrawn, are unsuitable
Steroids?

The patient should have evidence of ARDS and require an FiO2 \( \geq \) 50%.

The MEDURI steroid regimen:
- Loading dose 2mg/kg
- Then 2mg/kg/day from day 1 to 14
- Then 1mg/kg/day from day 15 to 21
- Then 0.5mg/kg/day from day 22 to 28
- Then 0.25mg/kg/day on days 29 and 30
- Finally 0.125mg/kg on days 31 and 32.
Proning?
PROs
1. Relieves the cardiac and abdominal compression exerted on the lower lobes
2. Makes regional Ventilation/Perfusion ratios and chest elastance more uniform
3. Facilitates drainage of secretions
4. Potentiates the beneficial effect of recruitment maneuvers
Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaële Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group®
Study Overview

- Placing patients who require mechanical ventilation in the prone rather than the supine position improves oxygenation.

- In this trial, the investigators found a benefit with respect to all-cause mortality with this change in body position in patients with severe ARDS.
characteristics of the participants at inclusion in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Supine Group (N=229)</th>
<th>Prone Group (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>60±16</td>
<td>58±16</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>152 (66.4)</td>
<td>166 (70.0)</td>
</tr>
<tr>
<td>Setting from which patient was admitted to ICU — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency room</td>
<td>98 (42.8)</td>
<td>101 (42.6)</td>
</tr>
<tr>
<td>Acute care facility</td>
<td>87 (38.0)</td>
<td>86 (36.3)</td>
</tr>
<tr>
<td>Home</td>
<td>26 (11.6)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>ICU</td>
<td>9 (3.9)</td>
<td>11 (4.6)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (3.9)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>McCabe score — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>183 (79.9)</td>
<td>197 (83.1)</td>
</tr>
<tr>
<td>B</td>
<td>45 (19.7)</td>
<td>39 (16.5)</td>
</tr>
<tr>
<td>C</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Coexisting conditions — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>39 (17.0)</td>
<td>50 (21.1)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>12 (5.2)</td>
<td>10 (4.2)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>16 (7.0)</td>
<td>15 (6.3)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>24 (10.5)</td>
<td>24 (10.1)</td>
</tr>
<tr>
<td>Cancer</td>
<td>30 (13.1)</td>
<td>24 (10.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>29 (12.7)</td>
<td>23 (9.7)</td>
</tr>
<tr>
<td>Immunodeficiency — no. (%)</td>
<td>38 (16.6)</td>
<td>32 (13.5)</td>
</tr>
<tr>
<td>SAPS II‡</td>
<td>47±17</td>
<td>45±15</td>
</tr>
<tr>
<td>Sepsis — no. total no. (%)§</td>
<td>195(229 (85.2)</td>
<td>194(236 (82.2)</td>
</tr>
<tr>
<td>SOFA score§</td>
<td>10.4±3.4</td>
<td>9.6±3.2</td>
</tr>
<tr>
<td>ARDS due to pneumonia</td>
<td>133 (58.1)</td>
<td>148 (62.4)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29±7</td>
<td>28±6</td>
</tr>
<tr>
<td>Other interventions — no. total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressors</td>
<td>190(229 (83.0)</td>
<td>172(237 (72.6)</td>
</tr>
<tr>
<td>Neuromuscular blockers</td>
<td>186(226 (82.3)</td>
<td>212(233 (91.0)</td>
</tr>
<tr>
<td>Renal-replacement therapy</td>
<td>39(228 (17.1)</td>
<td>27(237 (11.4)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>101(225 (44.9)</td>
<td>91(230 (39.8)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences between the groups in any of the characteristics listed, with the exception of the Sepsis-related Organ Failure Assessment (SOFA) score, the use of vasopressors, and the use of neuromuscular blockers. ARDS denotes the acute respiratory distress syndrome. COPD chronic obstructive pulmonary disease, and ICU intensive care unit. A version of this table with additional information is available as Table S2 in the Supplementary Appendix.

† A McCabe score of A indicates no underlying disease that compromises life expectancy, B an estimated life expectancy with the chronic disease of less than 5 years, and C an estimated life expectancy with the chronic disease of less than 1 year.

§ The Simplified Acute Physiology Score (SAPS II) ranges from 0 to 164, with higher scores indicating greater severity of symptoms.

¶ Sepsis was defined according to the American-European Consensus Conference criteria.

‖ SOFA scores range from 0 to 24, with higher scores indicating more severe organ failure.

| The body mass index is the weight in kilograms divided by the square of the height in meters. |
Ventilator Settings, Respiratory-System Mechanics, and Results of Arterial Blood Gas Measurements at the Time of Inclusion in the Study.


<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine Group (N = 229)</th>
<th>Prone Group (N = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (ml)</td>
<td>381±66</td>
<td>384±63</td>
</tr>
<tr>
<td>Tidal volume (ml per kg of PBW)</td>
<td>6.1±0.6</td>
<td>6.1±0.6</td>
</tr>
<tr>
<td>Respiratory frequency (breaths per min)</td>
<td>27±5</td>
<td>27±5</td>
</tr>
<tr>
<td>PEEP (cm of water)</td>
<td>10±4</td>
<td>10±3</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.79±0.16</td>
<td>0.79±0.16</td>
</tr>
<tr>
<td>Pplat (cm of water)</td>
<td>23±5</td>
<td>24±5</td>
</tr>
<tr>
<td>Cst (ml per cm of water)</td>
<td>35±15</td>
<td>36±23</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>80±18</td>
<td>80±19</td>
</tr>
<tr>
<td>Pao2/FIO2 (mm Hg)</td>
<td>100±20</td>
<td>100±30</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>52±32</td>
<td>50±14</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.30±0.10</td>
<td>7.30±0.10</td>
</tr>
<tr>
<td>Plasma bicarbonate (mmol per liter)</td>
<td>25±5</td>
<td>25±5</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Cst denotes static compliance of the respiratory system, FIO2 the fraction of inspired oxygen, Paco2 partial pressure of arterial carbon dioxide, Pao2 partial pressure of arterial oxygen, PBW predicted body weight. PEEP positive end-expiratory pressure, and Pplat end-inspiratory plateau pressure of the respiratory system.
† Data are for 227 participants in the supine group and 236 participants in the prone group.


The NEW ENGLAND JOURNAL OF MEDICINE
Kaplan-Meier Plot of the Probability of Survival from Randomization to Day 90.

Primary and Secondary Outcomes According to Study Group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Supine Group (N = 229)</th>
<th>Prone Group (N = 237)</th>
<th>Hazard Ratio or Odds Ratio with the Prone Position (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>Not adjusted</td>
<td>75 (32.8 [26.4–38.6])</td>
<td>38 (16.0 [11.3–20.7])</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted for SOFA score†</td>
<td>0.42 (0.26–0.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 90</td>
<td>Not adjusted</td>
<td>94 (41.0 [34.6–47.4])</td>
<td>56 (23.6 [18.2–29.9])</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted for SOFA score†</td>
<td>0.48 (0.32–0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful extubation at day 90 — no., total no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>145/223 (65.0 [56.7–71.3])</td>
<td>186/231 (80.5 [75.4–85.6])</td>
<td></td>
<td></td>
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<tr>
<td>Time to successful extubation, assessed at day 90 — days</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>19±21</td>
<td>17±16</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Non-survivors</td>
<td>16±11</td>
<td>18±14</td>
<td></td>
<td></td>
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<tr>
<td>Length of ICU stay, assessed at day 90 — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>26±27</td>
<td>24±22</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Non-survivors</td>
<td>18±13</td>
<td>21±20</td>
<td></td>
<td></td>
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<tr>
<td>Ventilation-free days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>10±10</td>
<td>14±9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>At day 90</td>
<td>43±38</td>
<td>57±34</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax — no. (% [95% CI])</td>
<td>13 (5.7 [3.9–7.5])</td>
<td>15 (6.3 [4.9–7.7])</td>
<td></td>
<td>0.89 (0.39–2.02)</td>
</tr>
<tr>
<td>Noninvasive ventilation — no./ total no. (% [95% CI])</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>At day 28</td>
<td>10/212 (4.7 [3.9–5.5])</td>
<td>4/228 (1.8 [0.9–3.5])</td>
<td>0.36 (0.07–3.50)</td>
<td>0.11</td>
</tr>
<tr>
<td>At day 90</td>
<td>3/206 (1.5 [0.2–3.2])</td>
<td>4/225 (1.8 [0.9–3.5])</td>
<td>1.22 (0.23–6.97)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tracheostomy — no./total no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>12/229 (5.2 [2.3–8.1])</td>
<td>9/237 (3.8 [1.4–6.0])</td>
<td>0.71 (0.27–1.86)</td>
<td>0.37</td>
</tr>
<tr>
<td>At day 90</td>
<td>18/223 (8.1 [4.5–11.7])</td>
<td>15/235 (6.4 [3.3–9.5])</td>
<td>0.78 (0.36–1.67)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Hazard ratios are shown for mortality and successful extubation; odds ratios are shown for other outcomes. CI denotes confidence interval.
†There were no significant differences between the groups in organ dysfunction as assessed from the SOFA score (Table 5A in the Supplementary Appendix).
Conclusions

• In patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28-day and 90-day mortality.
'Alternative' ventilator manipulations and modes
1. Conventional +
2. Non HFOV
3. HFOV
In conclusion............