ICU management of the Acute Respiratory Distress Syndrome

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Acute Respiratory Distress Syndrome

- High-permeability type pulmonary edema
- Acute onset
- \( \text{PaO}_2/\text{FiO}_2 < 200 \text{ mmHg} \)
- Bilateral infiltrates
- No history / sign of left ventricular dysfunction

\[ \text{TABLE 2. CLINICAL DISORDERS ASSOCIATED WITH THE DEVELOPMENT OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.} \]

<table>
<thead>
<tr>
<th>DIRECT LUNG INJURY</th>
<th>INDIRECT LUNG INJURY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common causes</strong></td>
<td><strong>Common causes</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
<td>Severe trauma with shock and multiple transfusions</td>
</tr>
<tr>
<td><strong>Less common causes</strong></td>
<td>Less common causes</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Fat emboli</td>
<td>Drug overdose</td>
</tr>
<tr>
<td>Near-drowning</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Inhalational injury</td>
<td>Transfusions of blood products</td>
</tr>
<tr>
<td>Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy</td>
<td></td>
</tr>
</tbody>
</table>

Reviewing 40 years of ARDS research

What did we learn?

• Pathophysiology:
  – Animal models: relevance?
  – A complex entity
Reviewing 40 years of ARDS research

**What did we learn?**

- **Pathophysiology:**
  - Animal models: relevance?
  - A complex entity

- **Clinical evaluation**
  - Pulmonary / extrapulmonary ARDS
  - Early / late ARDS
  - Other failing organs: a systemic disease?
**ARDS: pulmonary or systemic disease?**

<table>
<thead>
<tr>
<th>Table 5. Organ Dysfunction on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Organ dysfunction related to acute illness</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Septic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Organ failure (other than lung failure)</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Cardiac/hemodynamic</td>
</tr>
<tr>
<td>Hepatic</td>
</tr>
<tr>
<td>Positive inotropic support</td>
</tr>
<tr>
<td>Hemofiltration/dialysis</td>
</tr>
<tr>
<td>Organ dysfunction related to chronic underlying disease</td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Hepatic</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Ullrich, Anesthesiology 2000
## Stratification System of Acute Lung Injury

**Letter** | **Meaning** | **Scale** | **Definition** |
---|---|---|---|
G | Gas exchange | 0 | \( \text{PaO}_2/\text{FiO}_2 \geq 301 \) |
G | Gas exchange | 1 | \( \text{PaO}_2/\text{FiO}_2 \ 201-300 \) |
G | Gas exchange | 2 | \( \text{PaO}_2/\text{FiO}_2 \ 101-200 \) |
G | Gas exchange | 3 | \( \text{PaO}_2/\text{FiO}_2 \leq 100 \) |
G | Gas exchange (to be combined) | A | spontaneous breathing, ZEEP |
G | Gas exchange (to be combined) | B | assisted breathing, PEEP 0-5 cm\( \text{H}_2\text{O} \) |
G | Gas exchange (to be combined) | C | assisted breathing, PEEP 6-10 cm\( \text{H}_2\text{O} \) |
G | Gas exchange (to be combined) | D | assisted breathing, PEEP \( \geq 10 \) cm\( \text{H}_2\text{O} \) |
O | Organ failure | 0 | lung only |
O | Organ failure | 1 | lung + 1 organ |
O | Organ failure | 2 | lung + 2 organs |
O | Organ failure | 3 | lung + \( \geq 3 \) organs |
C | Cause | 0 | unknown |
C | Cause | 1 | direct lung injury |
C | Cause | 2 | indirect lung injury |
A | Associated disease | 0 | no disease causing death within 5 years |
A | Associated disease | 1 | coexisting disease (prognosis 6 m- 5 y) |
A | Associated disease | 2 | coexisting disease (prognosis < 6 months) |
Reviewing 40 years of ARDS research

What did we learn?

• Pathophysiology:
  – Animal models: relevance?
  – A complex entity

• Clinical evaluation
  – Pulmonary / extrapulmonary ARDS
  – Early / late ARDS
  – Other failing organs: a systemic disease?

• Specific treatment: no breakthrough!
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
<th>Type of Study</th>
<th>No. of Patients</th>
<th>Findings</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids (during the acute phase)</td>
<td>1987</td>
<td>Phase 3</td>
<td>87</td>
<td>No benefit</td>
<td>Bernard et al.¹²⁶</td>
</tr>
<tr>
<td>Glucocorticoids (during the acute phase)</td>
<td>1988</td>
<td>Phase 3</td>
<td>59</td>
<td>No benefit</td>
<td>Luce et al.¹²⁷</td>
</tr>
<tr>
<td>Alprostadil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>1989</td>
<td>Phase 3</td>
<td>100</td>
<td>No benefit</td>
<td>Bone et al.¹²⁴</td>
</tr>
<tr>
<td>Liposomal</td>
<td>1999</td>
<td>Phase 3</td>
<td>350</td>
<td>Stopped for lack of efficacy</td>
<td>Abraham et al.¹²³</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1996</td>
<td>Phase 3</td>
<td>725</td>
<td>No benefit; new preparations and methods of delivery now being studied</td>
<td>Anzueto et al.¹¹⁶</td>
</tr>
<tr>
<td>Glucocorticoids during the fibrosing-alveolitis phase</td>
<td>1998</td>
<td>Phase 3</td>
<td>24</td>
<td>Decreased mortality, but study was small</td>
<td>Meduri et al.¹³¹</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>1998</td>
<td>Phase 2</td>
<td>177</td>
<td>No benefit</td>
<td>Dellinger et al.¹¹⁹</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>1999</td>
<td>Phase 3</td>
<td>203</td>
<td>No benefit</td>
<td>Payen et al.¹²⁰</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>2000</td>
<td>Phase 2</td>
<td>234</td>
<td>No benefit</td>
<td>NIH Acute Respiratory Distress Syndrome Network¹³²*</td>
</tr>
<tr>
<td>Procysteine</td>
<td>1998</td>
<td>Phase 3</td>
<td>214</td>
<td>Stopped for lack of efficacy</td>
<td>Bernard G: unpublished data</td>
</tr>
<tr>
<td>Lisofylline</td>
<td>1999</td>
<td>Phase 2–3</td>
<td>235</td>
<td>Stopped for lack of efficacy</td>
<td>Unpublished data</td>
</tr>
</tbody>
</table>
Corticosteroids for Early ARDS

Corticosteroids should not be used in early ARDS.
Consider supplementation of septic patients with relative adrenal insufficiency.

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**Table 1. Clinical trials of glucocorticoids for acute respiratory distress syndrome (ARDS) prevention or early ARDS resolution**

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Population (n)</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprung et al. (37)</td>
<td>Septic shock (58)</td>
<td>MPS 30 mg/kg vs. Dex 6 mg/kg</td>
<td>Greater progression to ARDS with steroids (64% vs. 34%; ( p = .008 ))</td>
</tr>
<tr>
<td>Weigelt et al. (39)</td>
<td>Septic shock (84)</td>
<td>MPS 30 mg/kg every 6 hrs ( \times 2 ) days</td>
<td>Greater progression to ARDS (64% vs. 38%; ( p = .001 )) with no change in mortality rate (46% vs. 31%; ( p = .177 )) with MPS vs. placebo</td>
</tr>
<tr>
<td>Luce et al. (38)</td>
<td>Septic shock (87)</td>
<td>MPS 30 mg/kg every 6 hrs ( \times 4 ) doses</td>
<td>Similar progression to ARDS (34% vs. 38%) and overall mortality rate (58% vs. 54%) for MPS vs. placebo</td>
</tr>
<tr>
<td>Bernard et al. (40)</td>
<td>Established ARDS (99)</td>
<td>MPS 30 mg/kg every 6 hrs ( \times 4 ) doses</td>
<td>Similar mortality rate for MPS vs. placebo (60% vs. 63%)</td>
</tr>
</tbody>
</table>

MPS, methylprednisolone; DEX, dexamethasone.
## Corticosteroids for Late ARDS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Survival</th>
<th>Daily dose</th>
<th>Schedule</th>
<th>Tapering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashbaugh</td>
<td>1985</td>
<td>10</td>
<td>80 %</td>
<td>4-8 mg/kg</td>
<td>1-2 mg/kg q6</td>
<td>after D5 for 21 days</td>
</tr>
<tr>
<td>Hooper</td>
<td>1990,96</td>
<td>26</td>
<td>81 %</td>
<td>0.5-1 g/day</td>
<td>125-250 mg q6</td>
<td>after D3-D4 as tolerated</td>
</tr>
<tr>
<td>Meduri</td>
<td>1991,94</td>
<td>25</td>
<td>76 %</td>
<td>2-3 mg/kg</td>
<td>0.5-0.75 mg/kg q6</td>
<td>after extubation or D14</td>
</tr>
<tr>
<td>Biffl</td>
<td>1995</td>
<td>6</td>
<td>83 %</td>
<td>4-8 mg/kg</td>
<td>1-2 mg/kg q6</td>
<td>clinical response</td>
</tr>
<tr>
<td>Meduri</td>
<td>1998</td>
<td>24</td>
<td>88 %</td>
<td>2 mg/kg x14 d</td>
<td>0.5 mg/kg q6 x14 d</td>
<td>after D14, D21, D28 to D32</td>
</tr>
</tbody>
</table>
Effect of Prolonged Methylprednisolone Therapy in Unresolving Acute Respiratory Distress Syndrome

G. Umberto Meduri, MD; A. Stacey Headley, MD; Emmel Golden, MD; Stephanie J. Carson, RN; Rebe A. Umberger, RN; Tiffany Kelso, PharmD; Elizabeth A. Tolley, PhD

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Methylprednisolone</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors of ICU admission, No. (%)</td>
<td>16 (100)</td>
<td>3 (37)</td>
<td>.002</td>
</tr>
<tr>
<td>Survivors of hospital admission, No. (%)</td>
<td>14 (87)</td>
<td>3 (37)</td>
<td>.03</td>
</tr>
<tr>
<td>Death associated with unresolving ARDS, No.†</td>
<td>0 of 2</td>
<td>5 of 5</td>
<td>NA</td>
</tr>
<tr>
<td>MODS-free days by study day 28, mean (SEM)‡</td>
<td>16 (2)</td>
<td>6 (2)</td>
<td>.005</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, median, d</td>
<td>11.5</td>
<td>23</td>
<td>.001</td>
</tr>
<tr>
<td>Complications</td>
<td>Methylprednisolone*</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>New infections†</td>
<td>24</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Pneumonia‡</td>
<td>9 (38)</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>Sinusitis§</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>3 (12)</td>
<td>3 (30)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (17)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>2 (8)</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>Candidemia</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

- **4 after ICU discharge**
- **4 after crossover to MP**
Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

- Alive, methylprednisolone
- Alive, placebo
- Breathing without assistance, methylprednisolone
- Breathing without assistance, placebo

N=180
Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome
The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*
Decreased ARDS mortality
- the Success of ICU Management -

- Abraham
- Ullrich
- NIH ARDSNet
- Brower
- Ranieri
- Amato
- Zapol
- Bell
- Sloane
- Villar
- Bone
- Bernard
- Amato
- Brochard
- Ranieri
- NIH ARDSNet
- Abraham

Mortality (%) vs. Year (1975-2000)
Treatment Strategies for ARDS

- Treat ARDS etiology +++
  - Suspected H5N1 infection: oseltamivir
  - Community-acquired pneumonia

- Improve O$_2$ delivery and support failing organs
  - Hemodynamics
    - Fluid resuscitation
    - Vasopressors & inotropes
  - Renal function

- Nutritional support
Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Guidelines for Management

A. Initial resuscitation
B. Diagnosis
C. Antibiotic therapy
D. Source control
E. Fluid therapy
F. Vasopressors
G. Inotropic therapy
H. Steroids
I. rH Activated Protein C
J. Blood product administration
K. Mechanical Ventilation of Sepsis-induced ALI & ARDS
L. Sedation, analgesia & NM blockade
M. Glucose control
N. Renal replacement
O. Bicarbonate therapy
P. Deep vein thrombosis
Q. Stress ulcer prophylaxis
R. Consideration for limitation of support
S. Pediatric considerations
Treat early

The New England Journal of Medicine

Treat everything

The New England Journal of Medicine

Treat well

The New England Journal of Medicine

Mechanical Ventilation
Mechanical ventilation for ARDS
- *Rationale for changes*

- The mechanical properties of the respiratory system are altered during ARDS
  - Decrease in FRC = reduced lung volume
  - Decrease in compliance
  - Increase in resistance
ARDS $\Rightarrow$ Increased lung tissue

*Found in dependent & nondependent lung regions*

Lung tissue:
- Extravascular lung water
- Thoracic blood volume
- Lung inflammation

L Puybasset et al, Intensive Care Medicine, 26, 857, 2001
ARDS ⇒ Decreased lung aeration

- Always present in inferior lobes
- Often missing in the dependent lobes

2 different situations:

- Focal ARDS
- Diffuse ARDS

*L Puybasset et al, Intensive Care Medicine, 26, 857, 2001*
Mechanical ventilation for ARDS

- Rationale for changes -

• The mechanical properties of the respiratory system are altered during ARDS
  – Decrease in FRC
  – Decrease in compliance
  – Increase in resistance

• ARDS lungs are heterogeneous

• Mechanical ventilation can injure the lung
Mechanical Ventilation for ARDS
- Setting the Goals -

• « Adequate » gas exchanges
  – SaO₂ 88-94 %
  – « Permissive » hypercapnia
  – pH>7.25

• Prevent ventilator-induced lung injury (VILI)
  – « Volutrauma »
  – « Biotrauma »
There are no convincing data indicating that any mode of ventilatory support is superior to others for ARDS patients.

Chest 1993; 104: 1833-1859
Mechanical ventilation for ARDS

• Which mode?
• Settings?
  – $V_T$ (ou $P_{plat}$)
  – FiO$_2$
  – PEEP
  – RR
  – I/E
VILI: How to estimate the risk?

- Overdistension
- Edema fluid accumulation
- Surfactant degradation
- High oxygen exposure
- Mechanical disruption
Reducing $V_T$ from 12 to 6 mL/kg decreases mortality in ARDS

NIH ARDS Network. NEJM 2000
Reducing $V_T$ from 12 to 6 mL/kg decreases mortality in ARDS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>GROUP RECEIVING LOWER TIDAL VOLUMES</th>
<th>GROUP RECEIVING TRADITIONAL TIDAL VOLUMES</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>

NIH ARDS Network. NEJM 2000
Interpretation of PRCTs in ARDS

NIH Amato

Stewart Brochard Brower

LL 95% CI
OR
UL 95% CI
Interpretation of PRCTs in ARDS

- Amato et al.
- Brochard et al.
- Stewart et al.
- Brower et al.
- N.I.H.
Interpretation of PRCTs in ARDS

![Graphs showing plateau pressure over days for different studies and the N.I.H. guideline.](Image)
Mechanical ventilation for ARDS

• Which mode?
• Settings?
  – $V_T$ (or $P_{\text{plat}}$)
  – $\text{FiO}_2$
  – PEEP
VILI: How to estimate the risk?

- Overdistension
  - Edema fluid accumulation
  - Surfactant degradation
  - High oxygen exposure
  - Mechanical disruption

- Atelectasis
  - Surfactant inhibition
  - Hypoxemia
  - Maldistribution of $V_T$
  - Repeated opening / closure
**Regional Recruitment and Inflation in ARDS**

![Graph showing recruitment at different PEEP levels]

**PEEP (cmH$_2$O)**
- 0: 21 ± 1.8
- 5: 26 ± 1.4
- 10: 31 ± 1.8
- 15: 38 ± 2.1
- 20: 46 ± 3.2

**Recruitment (g)**

**End inspiration**
- 0: *
- 5: *
- 10: *

**End expiration**
- 0: *
- 5: *
- 10: *

*Gattinoni, AJRCCM 1995*
How to set PEEP?

« PEEP trial »

- Stepwise ↑ of PEEP
- Evaluation criteria
  - Oxygenation ?
  - Compliance ?
  - Hemodynamics ?

**ARTERIAL OXYGENATION**
GOAL: $\text{PaO}_2$ 55-80 mm Hg or $\text{SpO}_2$ 88-95%

Use these $\text{FiO}_2$/PEEP combinations to achieve oxygenation goal.

<table>
<thead>
<tr>
<th>FiO2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>
PEEP / FiO₂ algorithms

• Reminder of the objectives
• Simple & « validated »

ARterial oxygenation
GOAL: PaO₂ 55-80 mm Hg or SpO₂ 88-95%
Use these FiO₂/PEEP combinations to achieve oxygenation goal.

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

Hi-PEEP/Lo-FiO₂ Study Group FiO₂

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>.30</th>
<th>.30</th>
<th>.30</th>
<th>.30</th>
<th>.30</th>
<th>.40</th>
<th>.40</th>
<th>.50</th>
<th>.50</th>
<th>.50-80</th>
<th>.80</th>
<th>.90</th>
<th>1.0</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>24</td>
</tr>
</tbody>
</table>
### Table 1. Summary of Ventilator Procedures in the Lower- and Higher-PEEP Groups.*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator mode</td>
<td>Volume assist/control</td>
</tr>
<tr>
<td>Tidal-volume goal</td>
<td>6 ml/kg of predicted body weight</td>
</tr>
<tr>
<td>Allowable combinations of PEEP and FiO₂†</td>
<td></td>
</tr>
<tr>
<td>Lower-PEEP group</td>
<td></td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.3  0.4  0.4  0.5  0.5  0.6  0.7  0.7  0.7  0.8  0.9  0.9  0.9  1.0</td>
</tr>
<tr>
<td>PEEP</td>
<td>5    5    8    8    10   10   10   14   14   14   16   18   18–24</td>
</tr>
<tr>
<td>Higher-PEEP group (before protocol changed to use higher levels of PEEP)</td>
<td></td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.3  0.3  0.3  0.3  0.3  0.4  0.4  0.4  0.5  0.5–0.8  0.8  0.9  1.0</td>
</tr>
<tr>
<td>PEEP</td>
<td>5    8    10   12   14   14   16   16   18   20   22   22   22–24</td>
</tr>
<tr>
<td>Higher-PEEP group (after protocol changed to use higher levels of PEEP)</td>
<td></td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.3  0.3  0.4  0.4  0.5  0.5–0.8  0.8  0.9  1.0</td>
</tr>
<tr>
<td>PEEP</td>
<td>12   14   14   14   16   16   18   20   22   22   22   22–24</td>
</tr>
</tbody>
</table>
### Table 2. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lower-PEEP Group (N=273)</th>
<th>Higher-PEEP Group (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49±17</td>
<td>54±17†</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>Race or ethnic group (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Black</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Other or not available</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>APACHE III score‡</td>
<td>91±30</td>
<td>96±33</td>
</tr>
<tr>
<td>Tidal volume (ml/kg of predicted body weight)</td>
<td>8.2±2.0</td>
<td>8.0±2.0</td>
</tr>
<tr>
<td>Minute ventilation (liters/min)</td>
<td>12.1±4.2</td>
<td>12.0±3.4</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>22.8±7.8</td>
<td>23.2±7.6</td>
</tr>
<tr>
<td>No. of nonpulmonary organ or system failures¶</td>
<td>1.0±0.9</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td>PaO₂:FiO₂</td>
<td>165±77</td>
<td>151±67¶</td>
</tr>
<tr>
<td>Cause of lung injury (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Sepsis</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Aspiration</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Trauma</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Multiple transfusions</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>
How to set PEEP?

« PEEP trial »
• Stepwise ↑ of PEEP
• Evaluation criteria
  • Oxygenation ?
  • Compliance ?
  • Hemodynamics ?

Lung mechanics

**ARTERIAL OXYGENATION**
GOAL: PaO₂ 55-80 mm Hg or SpO₂ 88-95%
Use these FiO₂/PEEP combinations to achieve oxygenation goal.

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>0.3</th>
<th>0.4</th>
<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>20-24</td>
</tr>
</tbody>
</table>
Interpretation of PRCTs in ARDS

Amato et al.

Days
0 2 4 6 8

PEEP (cmH\(_2\)O)

0 2 4 6 8

100
80
60
40
20
0

Survival (%)

Days after Randomization
0 10 20 30

Protective

P<0.001

Conventional

No. at Risk
Protective 29 25 20 18
Conventional 24 11 9 7

N.I.H.

Days
0 2 4 6 8

DAYS

Interpretation of PRCTs in ARDS
Relative risk of death vs. PEEP (cm H₂O)

- **n = 331**
- **P = 0.001**

The graph shows a decreasing trend in relative risk of death as PEEP increases, indicating a statistically significant difference at a P-value of 0.001.
Relative risk of death vs PEEP (cm H$_2$O)

$n = 331$
Relative risk of death vs. PEEP (cm H$_2$O) for $n = 331$.
**How to set PEEP?**

**« PEEP trial »**
- Stepwise ↑ of PEEP
- Evaluation criteria
  - Oxygenation?
  - Compliance?
  - Hemodynamics?

**ARTERIAL OXYGENATION**
GOAL: PaO₂ 55-80 mm Hg or SpO₂ 88-95%
Use these FiO₂/PEEP combinations to achieve oxygenation goal:

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td>0.4</td>
<td>5</td>
</tr>
<tr>
<td>0.4</td>
<td>8</td>
</tr>
<tr>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>0.7</td>
<td>12</td>
</tr>
<tr>
<td>0.7</td>
<td>14</td>
</tr>
<tr>
<td>0.7</td>
<td>14</td>
</tr>
<tr>
<td>0.8</td>
<td>14</td>
</tr>
<tr>
<td>0.9</td>
<td>14</td>
</tr>
<tr>
<td>0.9</td>
<td>16</td>
</tr>
<tr>
<td>0.9</td>
<td>18</td>
</tr>
<tr>
<td>1.0</td>
<td>20-24</td>
</tr>
</tbody>
</table>

Graph showing pressure changes with different PEEP levels.
How to set PEEP?
- a practical alternative -

- Hypothesis #1

There is a potential for alveolar recruitment during the acute phase of ARDS (< D2-D4).

- Hypothesis #2

PEEP keeps open unstable alveoli recruited during previous inspirations.

- Hypothesis #3

Effective alveolar recruitment improves oxygenation and enables to meet the SaO₂ goals while reducing FiO₂.
Decremental PEEP trials

- Volume difference can represent either recruited or de-recruited volume.
- CRF measurements during a decremental PEEP trial following a recruitment maneuver can identify:
  - the response to recruitment manoeuvre
  - the level of PEEP where de-recruitment occurs.
FRC-guided PEEP setting in ALI -1
FRC-guided PEEP setting in ALI -1

![Graph showing PEEP (cmH2O) vs. lung function parameters.](image)
FRC-guided PEEP setting in ALI -2
FRC-guided PEEP setting in ALI -2

Volume expansion
1500 mL saline serum
FRC-guided PEEP setting in ALI -2
Fluid Resuscitation Strategy in ARDS

- Hypoprotidemia predicts the development of ARDS and death in septic patients
- EVLW correlates with mortality in ARDS
- Fluid resuscitation may improve cardiac output and O₂ delivery
- Treatment with albumin + furosemide might decrease mortality in ARDS

Starling Equation

\[ J_v \propto (\pi_c - \pi_l) - (\pi_{pp} - \pi_{ip}) \]

\[ J_v = K_{tc} ([P_c - P_l] - \sigma_d [\pi_{pp} - \pi_{ip}]) \]

Volume ?
Fluid ?
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

<table>
<thead>
<tr>
<th>Measured intravascular pressure (mm Hg)</th>
<th>MAP &lt;60 mm Hg or a need for any vasopressor (except dopamine ≤5 μg/kg/min); consider correctable causes of shock first</th>
<th>MAP ≥60 mm Hg without vasopressors (except dopamine ≤5 μg/kg/min)</th>
<th>Average urinary output &lt;0.5 ml/kg/hr</th>
<th>Average urinary output ≥0.5 ml/kg/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP</td>
<td>PAOP&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative strategy</td>
<td>Liberal strategy</td>
<td>Conservative strategy</td>
<td>Liberal strategy</td>
<td></td>
</tr>
<tr>
<td>Range 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;13</td>
<td>&gt;18</td>
<td>&gt;18</td>
<td>&gt;24</td>
<td></td>
</tr>
<tr>
<td>Range 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13</td>
<td>15–18</td>
<td>13–18</td>
<td>19–24</td>
<td></td>
</tr>
<tr>
<td>Range 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–8</td>
<td>10–14</td>
<td>8–12</td>
<td>14–18</td>
<td></td>
</tr>
<tr>
<td>Range 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>&lt;10</td>
<td>&lt;8</td>
<td>&lt;14</td>
<td></td>
</tr>
</tbody>
</table>

1. Vasopressor<sup>f</sup> Fluid bolus<sup>f</sup>
2. Fluid bolus<sup>c</sup> Vasopressor<sup>f</sup>
3. KVO IV Dobutamine<sup>a</sup> Furosemide<sup>b,1,2,4</sup>
4. KVO IV Dobutamine<sup>a</sup>
5. Fluid bolus<sup>c</sup>
6. Fluid bolus<sup>c</sup>
7. KVO IV Dobutamine<sup>a</sup> Furosemide<sup>b,1,2,4</sup>
8. KVO IV Furosemide<sup>b,1,2,4</sup>
9. Fluid bolus<sup>c</sup>
10. Fluid bolus<sup>c</sup>
11. KVO IV Dobutamine<sup>a</sup> Furosemide<sup>b,1,2,4</sup>
12. KVO IV Dobutamine<sup>a</sup>
13. Fluid bolus<sup>c</sup>
14. Fluid bolus<sup>c</sup>
15. KVO IV Furosemide<sup>b,1,2,4</sup>
16. KVO IV Furosemide<sup>b,1,2,4</sup>
17. Liberal KVO IV
18. Conservative Furosemide<sup>b,1,2,4</sup>
19. Liberal fluid bolus
20. Conservative KVO IV
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*
Currently no reason to implement an algorithm-controlled fluid management strategy in ARDS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Conservative Group</th>
<th>Liberal Group</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days, No.</td>
<td>14.6 ± 0.5</td>
<td>12.1 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PEEP, cm H₂O</td>
<td>7.5 ± 0.3</td>
<td>8.2 ± 0.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Plateau pressure, cm H₂O</td>
<td>24.2 ± 0.6</td>
<td>25.7 ± 0.5</td>
<td>0.002</td>
</tr>
<tr>
<td>PaO₂/FIO₂</td>
<td>198 ± 8</td>
<td>183 ± 6</td>
<td>0.07</td>
</tr>
<tr>
<td>Oxygenation index‡</td>
<td>10.1 ± 0.8</td>
<td>11.8 ± 0.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Lung injury score§</td>
<td>2.03 ± 0.07</td>
<td>2.27 ± 0.06</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
• FiO₂ 1
• PEEP 16 cmH₂O
• Pplat 38 cmH₂O
• VT 330 ml, FR 25
- PaO₂ 45 mmHg
- PaCO₂ 112 mmHg
- pH 7.02
Optimised Ventilatory Strategies For Severe ARDS

• Heating chambers
• Closed suctioning systems
• Recruitment maneuvers, sight…
• Prone positioning
• NO
• HFO
Mechanical Ventilation for ARDS

Conclusions -1

• No specific treatment have been shown to be effective in the treatment of ARDS.

• No reason to use high-dose steroids in early / late ARDS

• Treat the cause of ARDS!
  – Consider early antimicrobial treatment for CAP and oseltamivir if suspicion of influenza infection

• Follow current guidelines for supportive treatment of patients with sepsis (i.e. Surviving Sepsis Campaign)
Mechanical Ventilation for ARDS

Conclusions - 2

- Mechanical ventilation can injure the lung in experimental and clinical conditions
  - Barotrauma!
  - Pulmonary edema
  - Biotrauma?

- Reduction of $V_T$ and tight control of $P_{plat}$ decrease mortality of ARDS.
Alveolar recruitment and PEEP levels optimized according to the etiology and the severity of ARDS (lung mechanics) may improve gas exchange and outcome.

The use of alveolar recruitment strategies mandates preload optimization and close hemodynamic monitoring.

Don’t forget « details »: suctioning, no HME,…and treat ARDS etiology !!!

Consider alternative strategies and multimodal therapies (DV, NO, HFO…).