Acute Respiratory Failure
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Acute Lung Injury/ARDS
New Definition for ARDS: The Berlin Definition

- ARDS is defined by consensus criteria
- Last updated in 1994 by the American-European Consensus Conference
- While AECC definition has served well, group of investigators met in 2011 to reconsider the definition
- Goal of clarifying some aspects of AECC criteria

ARDS Definition Task Force, JAMA 2012
Berlin Definition vs. AECC Definition

- Preserves the central features of prior definition:
  - PaO2/FiO2 ratio < 300
  - Bilateral radiographic opacities not primarily due to heart failure
- Elimination of term “acute lung injury”
  - Mild ARDS: PaO2/FiO2 ratio 201-300
  - Moderate ARDS: PaO2/FiO2 ratio 101-200
  - Severe ARDS: PaO2/FiO2 ratio ≤ 100
- Patients with ARDS must be on positive pressure ventilation with PEEP ≥ 5 cm H2O
- CPAP allowed for mild ARDS only

ARDS Definition Task Force, JAMA 2012

Berlin Definition: Clarifications from AECC Definition

- Acute onset = within one week of known insult
- Recommends assessment of cardiac function (e.g., echocardiogram) if no known ARDS risk factor
- Clarifies that ARDS may co-exist with volume overload
- Several additional features were considered for inclusion but ultimately discarded, as they did not add predictive value:
  - Radiographic severity, respiratory compliance, high PEEP, and high minute ventilation

ARDS Definition Task Force, JAMA 2012

Berlin Definition: Summary

- Essential elements of definition unchanged
- Elimination of term “ALI”
- Increased recognition of co-occurrence of ARDS and volume overload
- Requirement for PEEP is most significant change
  - May limit applicability to early ARDS in non-ventilated patients and to resource-limited settings

ARDS Definition Task Force, JAMA 2012
Overview

- New definition of ARDS: The Berlin Definition
- Neuromuscular blockers
- Deserving: PROSEVA trial
- Cisatracurium
- Weaning
- Timing neuromyopathy in ARDS
- Future therapies:
  - SVTAI: Nanowires
  - Mesodermal stem cells

Cisatracurium for Early Severe ARDS

- N=340
- P:F ratio < 150 on PEEP ≥ 5
- Within 48 h of presentation
- Cisatracurium for 48 h
  - Bolus followed by infusion of 37.5 mg/hr
  - HR for death 0.68 (0.48-0.98, p=0.04)
  - After adjustment for baseline imbalances

Neuromuscular Blockers: Key Points

- Mechanism of benefit unclear
- Decrease in VILI
- Survival curves separate late
- No increase in neuromyopathy observed
- Trial may be too small to detect this
- Benefits may be unique to cisatracurium
- Reinforces clinical practice of many senior intensivists
  - Consider when dyssynchrony is an issue
  - Repeat trial needed before extending to all severe ARDS
Overview

- New definition of ARDS: The Berlin Definition
- Neuromuscular blockers
- Proning: PROSEVA trial
- Gas exchange
- Weaning
- Lung re-education in ARDS
- Future therapies:
  - Extracorporeal membranes
  - Mesenchymal stem cells


Gattinoni et al. NEJM 2001


Mancebo J, et al. AJRCCM 2006
Meta-analysis of Prone Positioning Suggests Benefit in Severe ARDS

**INCLUSION CRITERIA:**
- Age ≥ 18 years
- Intubated for ARDS < 36 hours
- ARDS according to AECC criteria for minimum 12-24 hours
- AND severity criteria at that time
  - PaO2/FIO2 < 150 with FIO2 ≥ 0.6 + PEEP ≥ 5 cm H2O + VT 6 ml/kg IBW

**EXCLUSION CRITERIA:**
- Pregnancy
- Facial trauma
- Unstable spines or long bone fractures
- Patient already on iNO or ECMO
- MAP < 65 (vasopressor resistant)
- Vast majority of pts were on vasopressors

PROSEVA: Inclusion and Exclusion Criteria

Proning Protocol: Important Details

- Randomized 474 patients
- DOSE OF PRONING:
  - Time from randomization to first PP = 55 ± 55 minutes
  - PP daily duration = 17±3 hours
  - All patients ventilated with lung protective ventilation
- Criteria for cessation of daily proning:
  - FIO2 ≥ 150
  - PEEP ≤ 10
  - FID2 ≤ 0.60
  - All criteria persist after at least 4 hrs in supine position
Primary outcome: 28-d Mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sepsis Group (N = 220)</th>
<th>Prone Group (N = 220)</th>
<th>Hazard Ratio or Odds Ratio with 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality — any (%) or 28-d</td>
<td>71 (32.7; 26.4–39.0)</td>
<td>56 (25.5; 19.7–32.7)</td>
<td>0.58 (0.37–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for SOFA score</td>
<td>0.42 (0.26–0.66)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Mortality — any (%) or 96-h</td>
<td>84 (38.6; 31.2–46.4)</td>
<td>62 (28.2; 21.5–35.7)</td>
<td>0.44 (0.28–0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for SOFA score</td>
<td>0.48 (0.32–0.75)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints at 96-h — not included in the 28-d analysis</td>
<td>140 (63.1)</td>
<td>136 (61.9)</td>
<td>0.89 (0.61–1.30)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier Plot of Probability of Survival from Randomization to Day 96.
Should we prone all our patients?

- PROSEVA replicates trends seen in some prior proning studies
  - Magnitude of difference much greater than in prior studies, for unclear reasons
  - More complications in supine group than expected (e.g. 13% incidence of cardiac arrest)
  - Control mortality near expected for this severity
- Centers were highly experienced with proning: No adverse events attributed to repositioning
- Video available on NEJM.org
- Most patients were treated with neuromuscular blockers
- Study authors: “Needs to be replicated”

Overview

- New definition of ARDS: The Berlin Definition
- Neuromuscular blockers
- Proning: PROSEVA trial
- Statins
- Warning
  - Long-term outcomes in ARDS
- Future therapies:
  - PETAL Network
  - Mesenchymal stem cells

Statins: Ineffective for VAP

- Multicenter RCT in France
- Patients on mechanical ventilation for at least 2 days and suspected of having VAP using clinical score
- Simvastatin 60 mg vs. placebo
  - Started on same day as antibiotics
  - Stopped for futility after enrollment of 300 patients
- Planned to enroll 1000 patients
- Mortality 21% in simvastatin group, 15% in placebo; p=0.10

Papazian, JAMA 2013
Statins: Ineffective for ARDS

- Statins for Acutely Injured Lungs in Sepsis trial
- Multicenter RCT in US, NHLBI ARDS Network
- Patients with ARDS and suspected/confirmed infection plus SIRS
- Rosuvastain 40 mg/20 mg vs. placebo
- Stopped for futility after 745 patients enrolled
- No difference in mortality or ventilator-free days

Overview

- New definition of ARDS: The Berlin Definition
- Neocellular blockers
- Profiling: PROSEVA trial
- Steroids
- Weaning
- Long-term outcomes in ARDS
- Future therapies:
  - PETAL Network
  - Mesenchymal stem cells

Effect of Pressure Support vs Unassisted Breathing Through a Tracheostomy Collar on Weaning Duration in Patients Requiring Prolonged Mechanical Ventilation

- Patients transferred to LTACH for weaning from prolonged ventilation (>21 days)
- Randomized to either weaning with pressure support or trach collar
- Took 10 years to enroll 500 patients
**Trial Protocol Details**

- Began with 5 day “screening procedure”
- Pts placed on trach collar
- Those who did not develop respiratory distress during 5 days were considered weaned = 160 of the 500 patients!
- Trach collar group: Max 12 hrs on first day
- Rested on ACVC overnight
- On day 3, trial of up to 24 hours of TC
- Pressure support group:
  - Assessed three times daily for decrease in PSV settings
  - Decrease of 2 cm H2O when possible, no more than 6 cm/day
  - Once PSV < 6 cm H2O for at least 12 hrs, trial TC

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**Weaning Study: Major Findings**

- About 1/3 of patients transferred to LTACH for weaning were immediately weaned
- For the rest, trach collar trials superior to pressure support gradual reduction
- No difference in mortality between two groups
  - 51-55% at 6 months, 63% at 1 year
- Unblinded, long duration of trial
Overview

- New definition of ARDS: The Berlin Definition
- Neuromuscular blockers
- Breathing: PROSEVA trial
- Sepsis
- Weaning
- Long-term outcomes in ARDS
- Future therapies:
  - UTI-1: N-acetylcysteine
  - Mesenchymal stem cells

Long Term Outcomes of Lung Protective Ventilation

- Mortality in months years after ICU discharge is high
- Interventions that improve short-term outcomes do not always translate into long-term survival benefits
- Example: Corticosteroids in persistent ARDS, activated protein C in severe sepsis
- Impact of lung protective ventilation on longer term outcomes not known
- Observational study of 485 ARDS patients testing association between lung protective ventilation strategy and mortality at 2 years after ARDS onset
  - Four academic centers between 2004-2007

Needham DM et al, BMJ 2012

Long Term Outcomes of Lung Protective Ventilation

- Only 41% of ventilator settings were classified as “adherent” to lung protective ventilation
- Tidal volume ≤ 6.5 ml/kg predicted body weight
- Plateau pressure ≤ 30 cm water
- 37% of patients had no ventilator settings compatible with low tidal volume ventilation
- 86% of patients had less than half of settings adherent
- Mortality at 2 years was 64%
- After adjusting for other mortality predictors, risk of death over 2 years decreased by 3% for each additional “adherent” ventilator setting

Needham DM et al, BMJ 2012
Many patients with ARDS are not being ventilated with optimal lung-protective strategies. Survival benefit associated with lower tidal volumes appears durable. Observational study, so lung protective ventilation may be marker for other process of care variables. Confounding by indication: Sicker patients may be more difficult to ventilate with LTV. More efforts to disseminate and facilitate implementation of landmark critical care trials are needed.

**Take-Home Points: Lung Protective Ventilation and Long-Term Outcomes**

- Needham DM et al, BMJ 2012

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**Low Tidal Volumes for Everyone?**

Association Between Use of Lung Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome

- 20 articles
- 2822 participants
- Risk ratio for ARDS 0.33 (95% CI 0.23-0.47)
- Number needed to treat = 11
- Risk ratio for mortality 0.64 (95% CI 0.46-0.89)

Serpa Neto A et al, JAMA 2012; Ferguson ND et al, JAMA 2012

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**Low Tidal Volumes in OR**

- Multicenter double blind trial
- 400 adults undergoing abdominal surgery
- Randomized to lung protective ventilation (including PEEP, recruitment maneuvers) or nonprotective ventilation (10-12 cc/kg, 0 PEEP, no recruitment maneuvers)
- Composite endpoint: Major pulmonary and non-pulmonary complications
- Endpoint occurred in 10.5% of lung-protective group vs. 27.5% of controls; p=0.001
- Decrease in rates of intubation post-op, hospital LOS

Futier et al, NEJM 2013
Overview

- New definition of ARDS: The Berlin Definition
- Neuromuscular blockers
- Preoxygen: PROSEVA trial
- Glutamine
- Weaning
- Long-term outcomes in ARDS
- Future therapies:
  - PETAL Network
  - Mesenchymal stem cells

New ARDS Network

- Focused on prevention and early treatment
- PETAL:
  - Prevention and Early Treatment of Acute Lung Injury
- New network of 12 centers including UCSF beginning July 2014
- Trials will likely start Spring 2015

Mesenchymal Stem Cells for ARDS

- Bone marrow derived, from healthy adult donors
- Non-immunogenic, no HLA matching needed
- Administered in other clinical settings to >2000 patients
- Excellent efficacy in experimental models of ARDS, including large animal models, ex vivo human lung
- Mechanism: Release of paracrine factors, mitochondrial transfer
- Phase I trial just completed (n=9); no safety concerns
- Phase II enrollment ongoing now at UCSF and 3 other centers (Stanford, Mass. General, Pittsburgh)
- www.stemcellsards.ucsf.edu
• Berlin definition of ARDS leaves the essence of the syndrome largely unchanged, clarifies several aspects
• Proning and neuromuscular blockade may confer mortality benefit for severe ARDS
• For difficult to wean patients, trach collar may be best
• Low tidal volume ventilation remains under-utilized and has a durable mortality benefit – may be good for all ventilated patients
• Statins are not a cure-all
• New approaches to therapy are needed:
  • Stem cells are being tested
  • Focus on prevention and early treatment

Thank you!