ARDS and treatment strategies

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ARDS: Definitions

- History of predisposing condition
- Refractory hypoxaemia of acute onset
  - $\text{PaO}_2/\text{FiO}_2$ ratio:
    - $<40$ ALI
    - $<27$ ARDS
- Bilateral pulmonary infiltrates (CXR)
- Absence of left ventricular dysfunction

American-European Consensus Conference on ARDS
ARDS: Definitions

• The 1994 American-European Consensus Conference (AECC) definition has considerable issues regarding reliability and validity.....
ARDS: the Berlin Definition

• Using a consensus process, a panel of experts convened in 2011 (EISCM, ATS and SCCM) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance.

• Marco Ranieri, Gordon D. Rubenfeld, B. Taylor Thompson, Niall D. Ferguson, Ellen Caldwell, Eddy Fan, Luigi Camporota, and Arthur S. Slutsky,
ARDS: the Berlin Definition

• Proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia:
  – mild (PaO$_2$/FIO$_2$ 200 - 300 mm Hg),
  – moderate (PaO$_2$/FIO$_2$ 100 - 200 mm Hg),
  – severe (PaO$_2$/FIO$_2$ ≤ 100 mm Hg)

• and 4 ancillary variables for severe ARDS: radiographic severity,
  – respiratory system compliance (≤40 mL/cm H$_2$O),
  – positive end-expiratory pressure (≥10 cm H$_2$O),
  – corrected expired volume per minute (≥10 L/min).
The draft Berlin Definition was evaluated using meta-analysis of 4188 patients with ARDS from 4 multicenter trials and 269 patients with ARDS from 3 single-centre data sets.

The 4 ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition.
ARDS: the Berlin Definition

Severity related to outcome:

• Mortality
  – Mild - 27%; (CI, 24%-30%)
  – Moderate - 32%; (CI, 29%-34%)
  – Severe - 45%; (CI, 42%-48%), ($P < .001$)

• Duration of mechanical ventilation in survivors
  – Mild - 5 days [IQR], 2-11;
  – Moderate - 7 days [IQR, 4-14]
  – Severe - 9 days [IQR, 5-17] ($P < .001$).

• Predictive value for mortality improved:
  – Berlin Definition area under the receiver operating curve of 0.577 (95% CI, 0.561-0.593)
  – AECC 0.536 (95% CI, 0.520-0.553; $P < .001$).

Still some problems

- Too broad a church
- What is acute?
- Role of CXR?
- What of inflammation?
- What of heart failure?
- Epidemiological or clinical?

Ferguson, 2004; 2006
### PaO\(_2\) of 10 kPa

<table>
<thead>
<tr>
<th>FiO(_2)</th>
<th>PaO(_2)/FiO(_2) Ratio</th>
<th>ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8 (80% oxygen)</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>0.6 (60% oxygen)</td>
<td>16.7</td>
<td></td>
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<tr>
<td>0.4 (40% oxygen)</td>
<td>25</td>
<td></td>
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<tr>
<td>0.3 (30% oxygen)</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>0.26 (26% oxygen)</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>0.21 (air)</td>
<td>47.6</td>
<td></td>
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</tbody>
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### PaO\(_2\)/FiO\(_2\) ratio

- Normal: 47.6
- ARDS: 12.5, 16.7, 25, 33.3, 38.5, 47.6
ARDS: Treatment
ARDS: Treatment

- Oxygen therapy
- Treat cause
- Organ support
  - respiratory NIPPV/IPPV
  - cardiac myocardial depression/sepsis
- Other treatments
  - Ventilatory strategies, Oscillator, ECMO, Novolung, Paralysis, Steroids Nitric Oxide, [Statins, Interferon-β, Heliox, Surfactant, Antioxidants, immunomodulation..]
- Avoid mistakes
Controversies in Management

- What oxygen level?
- Which ventilation mode?
- What PEEP?
- When to CT?
- Rescue therapies: inverse ratio, prone, NO, >30 cmH$_2$O, oscillation, ECMO etc.
- What CO$_2$?
- Fluid management?
- What Hb?
- Drugs: neuromuscular blockers, steroids, sildenafil, interferon-beta, statins, beta$_2$ agonists, surfactant, …
- What mode to wean?
- When to tracheostomise?
- Future – oxygen / CO$_2$ removal and negative pressure ventilation?
• 20 medical centres 1996 - 1999, stopped after 3 years n=861 (proposed 1600).
• Compared TV 12ml/kg (plateau <50cmH₂O) versus TV 6ml/kg (plateau < 30cm H₂O).
• Relative reduction in mortality of 22% (absolute 9%: 31 vs 39.8%)
Problems (1)

- Unethical(?) exposure of controls to excess TV
- Not clear whether reduction in TV or reduction in plateau pressure or hypercapnic acidosis that conveys benefits
- Very wide scatter of TV and plateau pressure before trial entry
- Patients excluded from trial had significantly lower mortality than controls (Ferguson, 2005; Deans, 2005)
ARDS: Ventilatory protocol
The Baby Lung concept
PEEP and PV curves

- PEEP below UIZ – prevents over distension
- PEEP above the LIZ keeps lung open
Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*
High vs low PEEP: ALVEOLI trial

- 549 patients
- 6ml/kg TV, plateau pressure < 30 cm water
- Randomised to low or high PEEP.
- No difference in outcome.
Correct Level of PEEP: LOVE

Lung Open Ventilation Trial (Canada)

Primary endpoint: Hospital mortality

n=983, 30 centres
Inclusion: PF ratio <250

6 ml/kg VT

Plateau pressure <40 cm H₂O (LOVE)

Plateau pressure <30 cm H₂O
Correct Level of PEEP: LOVE

Lung Open Ventilation Trial (Canada)

LOVE group developed less refractory hypoxaemia and had less ‘rescue’ therapies

No change in primary endpoint

Concluded that strategy was safe
Correct Level of PEEP: Express

Prospective RCT, 37 French ICUs

Primary endpoint: Death at 28 days

Inclusion: PF ratio <300

6 ml/kg VT

‘Minimal distension’ – PEEP 5-9 cm H$_2$O

‘Maximal recruitment’ – PEEP increased to achieve plateau pressure 28-30 cm H$_2$O
Correct Level of PEEP: Express

Improved oxygenation in the high PEEP group

Increased ventilator-free days and organ supported days in high PEEP group

No change in primary or secondary endpoints
Correct Level of PEEP: Express

Subgroup analysis

In most hypoxic patients at start of trial there was improved mortality in the high PEEP group

??High PEEP in targeted groups??
High Frequency Oscillation (HFO)

- Oscar Trial – HTA funded UK mechanical ventilation trial
- normal 6 mls/kg <30 cm H2O vs High Frequency Oscillation
- Recruitment closed. @800 patients. Results November
Prone Ventilation

• Proseva Study

• not yet published but presented at EISCM congress.

• Fascinating French multi-centre (and one Spanish centre) study of proning for $\geq 16$ hrs/day in severe ARDS. 450-odd patients and a halving in mortality (from approx 31% to 16%).
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*
LET'S HAVE ONE MORE AND THEN WE'LL GO!!
Comparison of two fluid-management strategies

- **Cumulative fluid balance** during the first 7 days was:
  - 136+/-491 ml in the conservative group
  - 6992+/-502 ml in the liberal group (P<0.001).

- **During first 28 days conservative strategy improved**:
  - Oxygenation index \[\text{mean airway pressure} \times \text{FiO}_2 / \text{PaO}_2 \times 100\]
  - Lung injury score
  - Ventilator-free days (14.6+/-0.5 vs. 12.1+/-0.5, P<0.001)
  - Days off ICU (13.4+/-0.4 vs. 11.2+/-0.4, P<0.001)

- **Conservative group did not have any difference in**:
  - Prevalence of shock
  - Use of dialysis
ARDS: successful treatments

- cisatracurium paralysis improves survival in early ARDS - ACURASYS trial. Papazian et al NEJM
- 340 patients - ARDS within 48 hours
- 90-day mortality 31.6% vs 40.7%, $P=0.04$.
- Confined to those with P/F ratio of <16.
- More ventilator-free time, less other organ failure
- Muscle weakness similar.

- May work by facilitating lung-protective ventilation.
ARDS: Steroids??

- No benefit in early ARDS
- Now no evidence it improves survival in late ARDS
  - It does speed extubation (more reintubations)
  - ? Increase CIPN
- No improvement or deterioration by 7 days
  - exclude infection
  - methylprednisolone 0.5 mg/kg QDS
  - reduce at 14 days and tail off from day 21 to 32
  - stop early (day 14) if non-responder
Effect of Recombinant Surfactant Protein C–Based Surfactant on the Acute Respiratory Distress Syndrome

Roger G. Spragg, M.D., James F. Lewis, M.D., Hans-Dieter Walmrath, M.D., Jay Johannigman, M.D., Geoff Bellingan, M.D., Pierre-Francois Laterre, M.D., Michael C. Witte, M.D., Guy A. Richards, M.D., Gerd Rippin, Ph.D., Frank Rathgeb, M.D., Dietrich Häfner, M.D., Friedemann J.H. Taut, M.D., and Werner Seeger, M.D.
$\text{PO}_2/\text{FiO}_2$ ratio / time

$\text{PO}_2/\text{FiO}_2$ ratio

= Surfactant administered
Venticute Surfactant Trial: Outcome 1)
Ventilator Free days

Number of Ventilator Free Days

Number of Patients

Control
Surfactant

Number of Patients

0 1 to 7 8 to 14 15 to 21 22 to 26

Number of Ventilator Free Days
ARDs: other drugs

• Beta2 Agonists – BALTI 2 suspended
• Sildenafil – pulmonary hypertension and right heart failure
• Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction – The HARP-2 Trial
• Interferon Beta – Boosting endothelial CD73 and reducing lung leak – The Faron Trial
Pathogenesis

- Inflammation and vascular leak

How can we control the vascular leak and inflammation?

- Surfactant dysfunction

Failed

- Iatrogenic barotrauma driving further inflammation

In place: 6 mls/kg
Post-ischemic IFN-beta treatment prevents leakage of vascular beds in ALI (in vivo)

Mice: ALI induced by 30’ mesenteric artery ischemia.

Simultaneously with reperfusion, IFN-beta iv (20,000 units).

Five minutes prior euthanasia, FITC-dextran to measure lung leak.

(n=8-13±SEM).

Kiss et al. (2007)  
IFN-beta prevention of lung leakage is CD73 dependent
FPCLI001 patient recruitment

Screened (n=368) → Excluded (n=227) → Eligible (n=141) → Non-recruited (n=104) → Control Cohort (n=59) → Recruited (n=37)

Cohort 1: 0.44 μg (n=3)
Cohort 2: 4.4 μg (n=3)
Cohort 3: 10 μg (n=4)
Cohort 4: 22 μg (n=5)
Cohort 5: 10 μg (n=22)

Protocolised after each dose expansion, drug availability

Patients from two most active sites: UCLH and St. Mary’s

>48 hours, comorbidity, age,
Survival

A

All 37 IFN-β treated patients

B

All 26 OTD IFN-β treated patients

\[ p = 0.0069 \]

\[ p = 0.0165 \]
Negative Trials

- NO
- Continuous rotation
- Prostaglandin Inhibitors (Ketoconazole, Ibuprofen)
- Antioxidants (N-acetyl cysteine, procysteine, free radical scavengers)
- Almitrine

Not sure

- ECMO
- Oscillation
- Continuous supraglottic aspiration?