What is new in ARDS

Geoff Bellingan
Medical Director
University College Hospital
ARDS: Definitions

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

American-European Consensus Conference on ARDS

**Let's just do those sums...**

<table>
<thead>
<tr>
<th>PaO₂ of 10 kPa</th>
<th>PaO₂/FiO₂ ratio</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>- FiO₂ of 0.8 (80% oxygen)</td>
<td>12.5</td>
<td>ARDS</td>
</tr>
<tr>
<td>- FiO₂ of 0.6 (60% oxygen)</td>
<td>16.7</td>
<td>ARDS</td>
</tr>
<tr>
<td>- FiO₂ of 0.4 (40% oxygen)</td>
<td>25</td>
<td>ARDS</td>
</tr>
<tr>
<td>- FiO₂ of 0.3 (30% oxygen)</td>
<td>33.3</td>
<td>ALI</td>
</tr>
<tr>
<td>- FiO₂ of 0.26 (26% oxygen)</td>
<td>38.5</td>
<td>ALI</td>
</tr>
<tr>
<td>- FiO₂ of 0.21 (air)</td>
<td>47.6</td>
<td>normal</td>
</tr>
</tbody>
</table>
Despite worldwide acceptance this definition is hugely controversial

- Too broad a church
- What is acute?
- Why P/F <40 and <26.7?
- Role of CXR?
- What of inflammation?

- Epidemiological or clinical?

Ferguson, 2004; 2006
“Despite considerable effort, the committee could not reach a consensus on the order of events in the pathogenesis of acute lung injury and ARDS”

ARDS: Pathophysiology

INJURY

EXUDATION & INFLAMMATION

FIBROPROLIFERATION

SURVIVE    DIE
A TOP investigator studies the problem
Fibroproliferative activity of BAL within 24 hours of ARDS

70% 32%
that of 10% serum
# N-PCP a Better Predictor of Outcome… Within 24 h of Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n= 28)</th>
<th>Nonsurvivors (n= 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL</td>
<td>1.24 (0.60-3.42)</td>
<td>3.1 (1.8-11.4)</td>
<td>0.017</td>
</tr>
<tr>
<td>N-PCP-III, U/ml*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17.5 ± 7.1</td>
<td>22.4 ± 8.3</td>
<td>0.0419</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>32.7 ± 17.0</td>
<td>39.9 ± 17.0</td>
<td>0.128</td>
</tr>
<tr>
<td>PaO$_2$/FIO$_2$</td>
<td>13.6 ± 3.3</td>
<td>14.13 ± 3.4</td>
<td>0.183</td>
</tr>
<tr>
<td>Lung injury score</td>
<td>3.1 ± 0.6</td>
<td>3.55 ± 0.6</td>
<td>0.426</td>
</tr>
</tbody>
</table>
Haematoxylin/Eosin: Early
**ACE : D allele as a risk factor for ARDS**

### Genotype and allele frequency

<table>
<thead>
<tr>
<th></th>
<th>Genotype %</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>H</em></td>
<td><em>I</em></td>
</tr>
<tr>
<td><strong>ARDS n=84</strong></td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td><strong>CABG Control n=174</strong></td>
<td>23</td>
<td>52</td>
</tr>
<tr>
<td><strong>ICU Control n=88</strong></td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td><strong>Population Control n=340</strong></td>
<td>24</td>
<td>51</td>
</tr>
</tbody>
</table>
Small differences in genotype make big differences to phenotype
Pathogenesis

Injury

- Genetic predisposition
- Inflammatory cell recruitment
- Fibroblast activation

Repair

Fibrosis
ARDS Incidence

• 1972 National Heart and Lung Task Force = 75 per 100,000 inhabitants/year in USA

• 20 years later, first population studies = 1.5 - 4.5 per 100,000 /year in Europe.

• Using 1992 definitions, reported incidences =
  ARDS 13-23 per 100,000 /year
  ALI 18 per 100,000 /year

• Latest epidemiological figures
  ARDS 59 per 100,000 /year
  ALI 79 per 100,000 /year.

• ARDS: widespread, (>30,000/year in UK)
  massive socio-economic impact
  comparable to breast cancer, asthma, MI.
ARDS: Treatment

Caution
Water on road during rain.
ARDS: Treatment

- Oxygen therapy
- Treat cause
- Organ support
  - respiratory NIPPV/IPPV
  - cardiac myocardial depression/sepsis
- Other treatments
  - Ventilatory strategies, Paralysis, Nitric Oxide, Heliox, Steroids, 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 cmH₂O, oscillation, ECMO etc.
- What CO₂?
- Fluid management?

- What Hb?
- Drugs: steroids, beta₂ agonists, surfactant, neuromuscular blockers, sildenafil…
- What mode to wean?
- When to tracheostamise?
- Future – oxygen / CO₂ removal and negative pressure ventilation?
Hypoxaemia Kills

Mortality rises as PaO$_2$ falls below 10 kPa

Bellingan, Wunch, Young, Rowan ATS 2005
Hyperoxia Kills

• 100% oxygen results in:
  – Progressive damage to the pulmonary endothelium and epithelium.
  – Free radical release,
  – Capillary leak
  – Impaired surfactant function
  – Maldistribution of microcirculatory perfusion

Death

Welty-Wolf 1997
Tsai 2003
Huang 1995
Hyperoxia is dangerous across species

NATURE
Insects breathe discontinuously to avoid oxygen toxicity.

Hetz SK, Bradley TJ.

Targeted Oxygenation

Hypoxaemia is bad

Hyperoxia is bad
Is there one side of the balance better than the other????
• 20 medical centres 1996 - 1999, stopped after 3 years n=861 (proposed 1600).
• Compared TV 12ml/kg (plateau <50cmH$_2$O) versus TV 6ml/kg (plateau < 30cm H$_2$O).
• 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

Upper Inflection Zone
Lower Inflection Zone

Pressure
Volume
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 H\textsubscript{2}O (LOVE)

Plateau pressure <30 cm H\textsubscript{2}O
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\textsubscript{2}O

‘Maximal recruitment’ – PEEP increased to achieve plateau pressure 28-30 cm H\textsubscript{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 currently at well over 600 pts…target 802
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
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
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.
$$[\text{PO}_2/\text{FiO}_2] \text{ ratio / time}$$
Venticute Surfactant Trial: Outcome 2) Oxygenation

Treatment with surfactant increased significantly the area under the PaO$_2$/FiO$_2$ vs. time curve.
Venticute Surfactant Trial: Outcome

1) Ventilator Free days

<table>
<thead>
<tr>
<th>Number of Ventilator Free Days</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Control</td>
</tr>
<tr>
<td>1 to 7</td>
<td>Surfactant</td>
</tr>
<tr>
<td>8 to 14</td>
<td></td>
</tr>
<tr>
<td>15 to 21</td>
<td></td>
</tr>
<tr>
<td>22 to 26</td>
<td></td>
</tr>
</tbody>
</table>

Number of Patients

- Control: 110
- Surfactant: 30

Number of Ventilator Free Days
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?