ARDS
Are we any further ahead?

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Case Introduction

• Would we all recognize this patient on the ward?
• Would we put ARDS as one of his diagnoses?
• If he ends up in the ICU, what can you do for him? Will any of it make a difference?
• How well is he likely to do?

“Adult Respiratory Distress Syndrome”

“The acute onset of severe respiratory distress and cyanosis that was refractory to oxygen therapy and associated with diffuse CXR abnormality and decreased lung compliance”

Ashbaugh, Bigelow, Petty Lancet 1967

What is ARDS?

Adult Respiratory Distress Syndrome
Acute Respiratory Distress Syndrome
Acute Lung Injury

Why is a definition important?

Lung Injury Score

<table>
<thead>
<tr>
<th>INJURY</th>
<th>CRITERIA</th>
</tr>
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</table>
| Acute lung injury           | Acute onset  
Pao2/Paco2 < 300 mm Hg 
Bilateral pulmonary “infiltrates” on frontal chest radiograph 
Pulmonary artery wedge pressure ≤ 18 mm Hg (when measured) or no clinical evidence of left atrial hypertension |
| Adult respiratory distress syndrome | Acute onset  
Pao2/Paco2 < 200 mm Hg  
Bilateral pulmonary “infiltrates” on frontal chest radiograph 
Pulmonary artery wedge pressure ≤ 18 mm Hg (when measured) or no clinical evidence of left atrial hypertension |
**Chest X-Ray**

“It was felt that the chest radiographic infiltrates should be bilateral and should be consistent with pulmonary edema, and, importantly, it was felt that these infiltrates could sometimes be very mild.”

Bernard GR et al, AJRCCM 1994, 149:818

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**Inter-observer Variability in X-Ray Interpretation**

21 experts reviewed 28 films

- 43% of films: complete agreement
- 32% films: significant disagreement
- % consistent with ALI/ARDS: 36 7%

Rubenfeld et al Chest 118:566, 2000

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**ARDS/ALI Definition – Best we can do for now.**

<table>
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<td>Bilateral pulmonary &quot;infiltrates&quot; on frontal chest radiograph</td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery wedge pressure ≤ 20 mm Hg (when measured) or no clinical evidence of left atrial hypertension</td>
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*Rubenfeld et al Chest 118:566, 2000*

**ARDS**

A syndrome often progressive and characterized by distinct clinical, pathological and radiographic stages

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**Table 2. CLINICAL DISORDERS ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS SYNDROME**

<table>
<thead>
<tr>
<th>Direct Lung Injury</th>
<th>Indirect Lung Injury*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration of gastric contents</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Severe thoracic trauma</td>
<td>Severe non-thoracic trauma</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>Multiple long bone fractures</td>
</tr>
<tr>
<td>Diffuse pulmonary infection</td>
<td>Hypoperfusion shock</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Hypertransfusion</td>
</tr>
<tr>
<td>Viral</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>Drug overdose</td>
</tr>
<tr>
<td>Toxic gas (smoke) inhalation</td>
<td>Reperfusion injury</td>
</tr>
<tr>
<td>Near-drowning</td>
<td>Post-lung transplantation</td>
</tr>
<tr>
<td></td>
<td>Post-cardiopulmonary bypass</td>
</tr>
</tbody>
</table>

*Caused by activation of an acute, systemic inflammatory response with hematogenous delivery of inflammatory mediators to the lungs.*

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**Stages of ARDS**

1. Exudative (acute) phase - 0-4 days
2. Proliferative phase - 4-8 days
3. Fibrotic phase - >8 days
4. Recovery
Time Course of Evolution of ARDS

ARDS Physiology

Pulmonary pressure-volume curves: inflation and deflation / air vs saline.

Shunt

ARDS and Inflammation


Sstephen O. - ACUTE HYPOXEMIC RESPIRATORY FAILURE

\[ P_{A,O_2} \sim 140 \to 700 \]

\[ P_A,O_2 \sim 100 \to 850 \]

\[ P_{A,O_2} 27 \to 32 \]

\[ P_{A,O_2} 27 \to 32 \]

\[ P_{A,O_2} 40 \to 50 \]
Back to the Case at hand...

- Diagnoses: Severe CAP
  ARDS
  SIRS

- Initial management:
  Admitted
  Cultures
  Fluid (200 ml/hr NS)
  Oxygen
  Upright posture
  Good Antibiotics
ARDS - Treatment Principles

• Treat the primary problem!
• Physiologic Support
  • Of the lungs
  • Other organs
• Avoid Complications
  • Lung (barotrauma, VALI…)
  • Sepsis (pneumonia, other…)
  • Other (DVT, nutrition, ‘stress’ ulcers…)
• Disease Modifiers

How does the lung heal?

• Resorption of alveolar fluid
• Removal of alveolar protein
• Type II cell proliferation
• Resolution of inflammation

Lung Liquid Clearance and Na Transport

Treat the primary problem

• Infection – antibiotics, drainage
• Aspiration – prevent recurrence
• Drugs – identify culprit and avoid
• Fractures – operative fixation
• Pancreatitis – support, npo, +/- antibiotics

Physiologic support (lungs)

1. Adequate oxygenation
2. Adequate ventilation (CO2 removal)
3. Anticipate and prevent complications
Adequate oxygenation

1. Better Q relative to V
   - Pulmonary vasodilators (NO)
   - Increase cardiac output (fluid/other)

2. Better V relative to Q
   - PEEP
   - Inverse ratio ventilation
   - Recruitment maneuvers
   - Patient position

3. Fluid Management Overall – ‘dry lungs are happy lungs’

Optimal PEEP

Changes in PaO2, shunt (Qs/Qt), total compliance, and oxygen tension as values of PEEP higher and lower than an optimum level corresponding to best PEEP.

(Literature from Zapol WM and F. Lemaire, ADULT RESPIRATORY DISTRESS SYNDROME, Marcel Dekker, Inc., 1991)

Lung Overinflation

Effect of 45 cmH2O peak airway pressure ventilation of increasing duration on indices of pulmonary edema in rats. Extravascular lung water (ELW), dry lung weight (DLW), and the distributive space in lungs of I-labeled albumin (Alb. Space) progressively increased as ventilation was continued. After 20 min of mechanical ventilation, there was a dramatic increase in all edema indices (p < 0.01 versus other groups). Moreover, at this stage, proteinaceous material and fluid was regularly found in the trachea.

(Adapted from Dreyfuss et al., Am. Rev. Respir. Dis. 1985;132:880-884)

Respective effects of high-pressure-high-volume ventilation (HiP-HiV), low-pressure-high-volume ventilation (LoP-HiV, iron lung), and high-pressure-low-volume ventilation (HiP-LoV, thoracoabdominal strapping during 45 cmH2O IPPV). There was no edema in the animals that were not distended, but those with pulmonary distention presented high-permeability edema irrespective of airway pressure (p < 0.0001 versus controls).

(Reproduced from Dreyfuss et al., Am. Rev. Respir. Dis. 1988;137:1159-1164)

Tidal Ventilation at Low Airway Pressures: Lung Injury

Figure 1: Composite pressure-volume curves (lactate control) and after hemorrhage ventilation with different levels of PEEP

(Maurolo et al., Am J Respir Crit Care Med. 1996;154:1327-34)
Ventilation strategy and lung lavage cytokine concentrations


Injurious Ventilatory Strategies

PEEP generally opposes injury or edema formation (minus sign) except when it contributes to overinflation (plus sign).


Inspiratory P/V curve in an ARDS patient

Roupie E. et al AJRCCM 1995; 152: 121-128

NIH NHLBI ARDS Network

Prospective, Randomized, Multi-Center Trial of 12 ml/kg Vs 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

"Respiratory Management in ALI/ARDS"

Primary Endpoints

Mortality prior to hospital discharge with unassisted breathing.

Ventilator Free Days (VFDs)

Days alive, off mechanical ventilation between enrollment and day 28

Mortality Prior to Hospital Discharge

<table>
<thead>
<tr>
<th>Mortality (Percent)</th>
<th>6 ml/kg</th>
<th>12 ml/kg</th>
</tr>
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<tbody>
<tr>
<td>0.0054</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IL-6 and IL-8 are Significantly Decreased in Patients Ventilated with 6 ml/kg vs 12 ml/kg

**Optimal PEEP**

Changes in PaO₂, shunt (Qs/Qt), total compliance, and oxygen transport at values of PEEP higher and lower than an optimum level corresponding to best PEEP. (From Suter et al., N. Engl. J. Med. 1975;292:284-289.)


Mortality Before Hospital Discharge

‘Conventional’ Ventilation for ARDS – Current Approach

1. Avoid overdistension (VALI)- bw tidal volume (~6 ml/Kg), relatively higher RR
2. Avoid underdistension (atelectasis, cyclical airway collapse, VALI)- relatively high PEEP (theoretically > lower inflection point of P-V curve)
3. Try to ventilate on the deflation limb of P-V curve- recruitment maneuvers
4. Enough oxygen
5. Tolerate hypercapnia
Patient Position

- Lateral?
- Prone?
- Head of bed up?

Randomized Trial of Prone Positioning

Patient selection: patients with ALI/ARDS

Patients enrolled: 304: 152 each arm

Study protocol: prone position for > 6 hours each day for 10 days

Gattinoni NEJM 2001;345:568-573

Oxygenation Improved Modestly Prone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine</th>
<th>Prone</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2</td>
<td>8.5 +/- 27</td>
<td>15 +/- 26</td>
<td>0.04</td>
</tr>
<tr>
<td>FiO2</td>
<td>-7.6 +/-18</td>
<td>-12.7 +/-19</td>
<td>0.02</td>
</tr>
<tr>
<td>P/F ratio</td>
<td>44.6 +/-68</td>
<td>63 +/-67</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Gattinoni NEJM 2001;345:568-573

There Was No Improvement in Survival

- RCT NO in ARDS
- Transient improvement in oxygenation only

Michael J et al AJRCCM 1994

Shunting in ARDS and INO

- RCT NO in ARDS
- Transient improvement in oxygenation only

Michael J et al AJRCCM 1994
No in ARDS – NO effect on mortality

HFOV in ALI/ARDS

Patients enrolled:
148 with ARDS (P/F < 200 with PEEP > 10)

Patients randomized to:
Conventional ventilation or HFOV

Derdak S et al AJRCCM 166:801, 2002

HFOV Trial Outcomes

<table>
<thead>
<tr>
<th>Modality</th>
<th>N</th>
<th>30 day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFOV</td>
<td>75</td>
<td>28 (37%)</td>
</tr>
<tr>
<td>Conventional</td>
<td>73</td>
<td>38 (52%)</td>
</tr>
</tbody>
</table>

Derdak S et al AJRCCM 166:801, 2002

Pulmonary pressure-volume curves: inflation and deflation / air vs saline

Surfactant – Any Future?

- Possible reasons for failure of Exosurf:
  - Poor delivery system (aerosolized vs instilled directly)
  - Low dose
  - Lack of surfactant proteins
  - Inhibition of surfactant via alveolar/plasma proteins

- New surfactant preparations under active study
RCT of with ARDS of mean duration 9 days
24 patients over 2 years
Built in cross overs
“Sequential clinical trial”
One tailed hypothesis

New VAP
9/16 - steroid
1/8 - placebo
Bottom line = poor study
Ongoing NIH DB RCT (results likely 2005)

Outcomes versus Lung Liquid Clearance

Modulators of Lung Liquid Clearance (experimentally)

- Hormones
  - Beta agonists
  - Dopamine
  - Gluco and mineralocorticoids
- Growth Factors – KGF, EGF
- Gene Transfer – Na-K-ATPase

Lessons From Survivors

Excised human lung – beta agonists work
One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

- 109 survivors of ARDS (~93% of survivors)
- Patients evaluated in clinic 3, 6, and 12 months after ICU discharge
- Evaluation of symptoms, PFT’s, 6MWD, QOL (SF-36), return to work

Herridge M et al. NEJM 2003;348:683-693

With the Exception of DLCO, Lung Function Returns to Normal

Herridge M et al. NEJM 2003

Six Minute Walk Test Improved Over Time but Limitations Persisted

Herridge M et al. NEJM 2003

Short-Form General Health Score

Score
- Patients (3 months) 0
- Patients (12 months) 25
- Normal Subjects 84

49% of patients returned to work

Key limiting symptoms = fatigue, weakness (not respiratory)

Herridge M et al. NEJM 2003

Quality of Life Scores are Poor

Table II. Short-Form and 36-Item General Health Scores Among Survivors of the Acute Respiratory Distress Syndrome at 3 and 12 Months After ICU Discharge. Data are Mean (±SE).

Herridge M et al. NEJM 2003

Davidson TA et al. JAMA 1999, 28:354
Conclusions

- Patients who survive ARDS have persistent functional disability as measured by an abnormal 6 minute walk test and a low score on the SF-36.
- Muscle weakness and fatigue were major contributors to this disability.
- ?Etiology – steroid myopathy
  - critical illness neuromyopathy
  - disuse myopathy
  - weight loss...

Summary

- A definition of a syndrome is a key first step to understanding it
- We understand how lung injury develops much better than we understand how it resolves
- There is an increasing yet far from complete understanding of the influence of genetics on the incidence and outcome of ARDS
- Critical care is no longer just ‘physiologic support’ – the type of care influences outcome, including the potential for harm

Summary

- Mortality is improving – unclear why
- Outcome for survivors is good, but not as good as we previously thought (especially when we ask them!)
- We know more, but there is a long way to go
- Prediction - One day we will be able to modulate the recovery process from lung injury
- PS: The patient went home after 6 weeks of rehabilitation. He remains 'fatigued'.