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Acute Respiratory Distress Syndrome

Thomas H. Sisson M.D.
Division of Pulmonary and Critical Care

Winter 2009
Case Presentation:

Mrs. K is a 56 yo woman With Sickle Cell Trait and Known Cholelithiasis (Gall Stones) Transferred to UMMC For Respiratory Failure.

-8/3/06: 9/10 Abdominal Pain, Nausea and Vomiting.
-RUQ U/S Demonstrated Gall Stones and Evidence of Acute Cholecystitis.
-8/4/06: Surgery.
-8/5/06: POD #1, Unremarkable Recovery.
-8/6/06: POD #2, Altered Mental Status, Fevers (T-105.0F), Abdominal Pain. WBC - 31.7K, Amylase and Lipase Markedly Elevated. Abdominal CT Scan Reveals a Large Fluid Collection Around the Pancreas.
-8/7/07: POD #3, Hypotensive and Tachypnea. Mechanical Ventilation Initiated Secondary to Respiratory Distress. Transferred to UMMC.

Vent settings: Rate-12, Tidal Volume-500 ml, FiO2-60%
ABG: pH-7.38, pCO₂-28, pO₂-63, O₂ sat-88%
Chest X-ray: Bilateral Patchy Parenchymal Opacities

Does Mrs. K Have ARDS?
What is Acute Respiratory Distress Syndrome (ARDS)?

Injury

Disruption of Alveolar Capillary Membrane

Non-Cardiogenic Pulmonary Edema

Protein-rich Plasma Fluid

Hypoxemia

Decreased Compliance

Mortality

T. Sisson
# Clinical Risk Factors:

## Direct Lung Injury

**Common Causes**
- Pneumonia (Bacteria, Viruses, Fungi)
- Aspiration of Gastric Contents

**Uncommon Causes**
- Pulmonary Contusion
- Fat Embolism
- Amniotic Fluid Embolism
- Near-drowning
- Inhalational Injury (Smoke, NH₃)
- Reperfusion Injury after Transplant

## Indirect Lung Injury

**Common Causes**
- Sepsis
- Severe Trauma with Shock
- Acute Pancreatitis

**Uncommon Causes**
- Multiple Transfusions
- Drug Overdose
- Diffuse Intravascular Coagulation
Smoking Does Not Directly Cause ARDS
but May Increase Risk of Developing the Disorder
Pathogenesis of ARDS

**Insult**
- Infection, Aspiration, Trauma

**Intact Alveolus**

**Provisional Matrix**
- (Fibrin, Fibronectin, Proteoglycans)

**Diffuse Alveolar Damage**
- Formation of Provisional Matrix
- Entrapment of Surfactant
- Accumulation of Fibroblasts
- Loss of Functional Airspace

**Infiltration of Inflammatory Cells**
- Denudation of Epithelium
- Disruption of Alveolar Capillary Membrane
- Leak of Protein-rich Plasma Fluid
- Inactivation of Surfactant

**AM**

**PMN**

**AEC-II**

**Intact Alveolus**

**T. Sisson**
Pathogenesis of ARDS

- Repair
- Fibrosis
- Degraded Provisional Matrix
- Reconstitution of Epithelium
- Removal of Provisional Matrix
- Apoptosis of Fibroblasts
- Limiting Myofibroblast Differentiating

Impaired Re-epithelialization
Further Accumulation of Fibroblasts
Myofibroblast Differentiation
Deposition and Accumulation of Collagen

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Chest X-ray:  Alveolar Injury and Fluid Leak Results in Diffuse Bilateral Infiltrates

Source Undetermined
Chest CT Scan: Bilateral Infiltrates Are Heterogeneous
Evolution of Pathogenesis:

Exudative Phase (7 Days)  →  Proliferative Phase (14 Days)  →  Fibrotic Phase (21 Days)

Alveolar Wall Damage With Flooding  →  Type II Alveolar Cell Hyperplasia Myofibroblast Infiltration Resolution of Edema  →  Extensive Fibrosis With Loss of Normal Lung Architecture

↓↓ Pa0₂ ↓ Compliance Bilateral Infiltrates  ↓↓ Pa0₂ ↓ Compliance Bilateral Infiltrates  ↓↓ Pa0₂ ↓ Compliance Infiltrates ± Bullae

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How is ARDS Diagnosed?

**Clinical Diagnostic Criteria:**

- **Acute Onset:** 6-72 Hours (in setting of a risk factor).
- **Chest X-ray:** Diffuse Bilateral Infiltrates.
- **Hypoxemia.**
  - PaO$_2$/FiO$_2$ <300: Acute Lung Injury
  - PaO$_2$/FiO$_2$ <200: Acute Respiratory Distress Syndrome
  
  **Example:** PaO$_2$=60 on 50% FiO$_2$  P/F ratio= 120

- **Non-Cardiogenic Pulmonary Edema.**  PCWP <18
Differential Diagnosis of ARDS

Definition is Non-Specific:
Many Diseases Can Present Acutely With Bilateral Infiltrates and Hypoxemia

ARDS  CHF  Pneumonia  Alveolar Hemorrhage  Aspiration
### Differential Diagnosis for ARDS

**Clinical Respiratory Disress**

- \( \text{rr, \( \downarrow \)PaO}_2, \downarrow \text{PaCO}_2 \)

#### Acute Cardiac Event

- Low Flow: Cool Extremities
- S3 or S4 Gallop/Cardiomegaly
- Jugular Venous Distention
- Crackles (wet)

#### History

- High Flow: Warm Extremities
- No Gallop/No Cardiomegaly
- No Jugular Venous Distention
- Crackles (dry)
- Evidence of Risk Factor

#### Laboratory

- ECG: New or Old Infarct
- Chest Xray: Perihilar Infiltrates/ Effusions
- Cardiac Enzymes: Elevated
- PCWP>18mmHg

- ECG: Normal (Tachycardia)
- Chest Xray: Diffuse
- Cardiac Enzymes: Normal
- PCWP<18mmHg
## Case Presentation: Does our patient have ARDS?

### Clinical Diagnostic Criteria:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Onset: 6-72 Hours (risk factor)</td>
<td>Yes</td>
</tr>
<tr>
<td>Respiratory Failure Within 48 Hours of Pancreatitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest X-ray: Diffuse Bilateral Infiltrates</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoxemia: PaO₂/FIO₂ &lt;300: Acute Lung Injury</td>
<td>Yes</td>
</tr>
<tr>
<td>PaO₂/FIO₂ &lt;200: Acute Respiratory Distress Syndrome</td>
<td>Yes</td>
</tr>
<tr>
<td>PaO₂=63 on 60% FIO₂ = 63/0.6 = 105</td>
<td></td>
</tr>
<tr>
<td>Non-Cardiogenic Pulmonary Edema: PCWP &lt;18</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Management of ARDS:
Management of ARDS:

Problems

- Reduced Compliance & Loss of Lung Volume
- Impaired Oxygenation: V/Q Mismatch Shunting
- High Mortality

Mechanical Ventilation

TV and FiO2
Management of ARDS: Reduced Compliance

- Normal
- ARDS

Graph showing volume vs. pressure for normal and ARDS conditions.
Management of ARDS: Reduced Compliance

Volume

Pressure

X mL

Normal

ARDS

X cmH₂O

Y cmH₂O

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Management of ARDS: Reduced Compliance
Ventilator Associated Lung Injury (VALI)

- Over-Distention
- Volu- vs. Barotrauma
- Healing
- Pneumothorax
- Mortality

Graph:
- Pressure (Y cmH₂O)
- Volume (X ml)
- ARDS

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Management of ARDS: Reduced Compliance

Ventilator Associated Lung Injury (VALI)

Atelectasis

Over-Distention

Atelectasis

Source Undetermined

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Management of ARDS: Reduced Compliance

ARDS Network

6cc/kg Tidal Volume
12cc/kg Tidal Volume

Mortality Prior to Discharge
Ventilator Free Days

Volume

Pressure

ARDS

12cc/kg
6cc/kg
Management of ARDS: Reduced Compliance

Median Number of Ventilator Free Days In First 28 Days

Time (Days)
0 2 4 6 8 10 12 14

Treatment Groups
6cc/kg 12cc/kg

ARDSnet NEJM 2000
Management of ARDS: Reduced Compliance

Mortality at the Time of Hospital Discharge

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6cc/kg</td>
<td>30</td>
</tr>
<tr>
<td>12cc/kg</td>
<td>40</td>
</tr>
</tbody>
</table>

P = 0.0054

ARDSnet NEJM 2000
Management of ARDS: Reduced Compliance

Goal is Airway Pressure < 30 cmH₂O

ARDSnet NEJM 2000
Case Presentation:

48 Hrs After Transfer to UMMC, Our Patient (Wgt 70kg) Remains on Mechanical Ventilation With the Following Ventilator Settings:

Rate-33, Tidal Volume-420 ml (6 ml/kg),  FiO2-70%

Her Airway Pressure on This Tidal Volume is Measure at 38 cmH₂O.

What Should be Done Next?
Management of ARDS: Reduced Compliance

Volume

Pressure (cmH$_2$O)

ARDS

6cc/kg

5cc/kg
### Management of ARDS: Reduced Compliance

**Problem:** Low Tidal Volume Ventilation = Rapid Respiratory Rate

<table>
<thead>
<tr>
<th>Tidal Volume</th>
<th>Respiratory Rate</th>
<th>Minute Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12cc/kg</td>
<td>840cc</td>
<td>17/min</td>
</tr>
<tr>
<td>70kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6cc/kg</td>
<td>420cc</td>
<td>33/min</td>
</tr>
<tr>
<td>70kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5cc/kg</td>
<td>350cc</td>
<td>40/min</td>
</tr>
<tr>
<td>70kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Patient Specific**
  - **Tidal Volume**: Variable
  - **Respiratory Rate**: Variable
  - **Minute Ventilation**: 14000 ml

**Patient Discomfort**
- Breath Stacking

---

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Management of ARDS: Reduced Compliance

Rapid Respiratory Rate

- Patient Discomfort
- Breath Stacking
  - Increased Intra-Thoracic Pressure (AutoPEEP)
    - Hemodynamic Instability

ARDS Network

Respiratory Rate Limited to 35 Breaths/Minute

Sedation ± Paralysis
Management of ARDS: Reduced Compliance

- **Tidal Volume**: 5cc/kg
  - Low Volume: 350cc
  - 70kg

- **Respiratory Rate**: 35/min

- **Minute Ventilation**: 12,250ml
  - Actual
  - 14000ml
    - Required

If Actual MV < Required MV → ↑PaCO2 and ↓pH

**Permissive Hypercapnea**

Note: If pH Drops too Low, the Patient can Become Hypotensive
Management of ARDS: Reduced Compliance

Arterial PaCO₂

Time (days)

PaCO₂ (mmHg)

0 1 2 3 4 5

6cc/kg

12cc/kg

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Management of ARDS:

- Impaired Oxygenation: V/Q Mismatch
- Shunting
- Reduced Compliance
- High Mortality

Problems

Mechanical Ventilation
Management of ARDS: Impaired Oxygenation

Surfactant Inactivation

Atelectasis +

Alveolar Flooding

V/Q Mismatch + Shunting

Source Undetermined
Management of ARDS: Impaired Oxygenation

Low V/Q High V/Q Source Undetermined

Anterior

Shunt

Low V/Q

High V/Q

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Case Presentation:

Due to High Airway Pressures, Our Patient’s Ventilator Settings Have Been Changed To:

Rate-35, Tidal Volume-350 ml (5 cc/kg).

Her FiO2 Requirements Have Now Increased to 80%.

Her Airway Pressure on the Current Tidal Volume is Measured at 26 cmH₂O (see above).

Her ABG is: pH-7.33, pCO₂-48, pO₂-51, O₂ sat-88%

What Should be Done Next?
Management of ARDS: Impaired Oxygenation

Goal: Maintenance of Adequate Tissue Oxygenation

\[ DO_2 = CI \times (1.3 \times O_2\text{sat} \times HGB + 0.003 \times PaO_2) \]

PaO2 ≥ 55mmHg
O2 Sat ≥ 88

FI02 ≤ 50%

Note: High Levels of O2 Are Likely Toxic

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Management of ARDS: Impaired Oxygenation

**PEEP: Positive End-Expiratory Pressure**

- PEEP: Recruits Atelectatic Alveoli
- Correct Low V/Q
Management of ARDS: Impaired Oxygenation

PEEP Should be Adjusted to Maximize Oxygen Delivery and Not Simply $O_2$ Saturation

$$DO_2 = CI \times [(1.3 \times O_2 \text{ Sat} \times HGB) + (0.003)PaO_2]$$

Problem: High Levels of PEEP Can Impair Venous Return and Decrease CI

Perform a Best PEEP Titration
Management of ARDS: Impaired Oxygenation

Best PEEP Titration: Maximize $DO_2 = CI \times (1.3 \times O_2 \text{ Sat} \times HGB)$

Example: $FIO_2=80\%$ and $O_2 \text{ Saturation} = 86\%$

<table>
<thead>
<tr>
<th>PEEP</th>
<th>O2 Saturation</th>
<th>Cardiac Index</th>
<th>$O_2 \text{ Sat} \times CI$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>86%</td>
<td>3.5</td>
<td>3.01</td>
</tr>
<tr>
<td>12</td>
<td>88%</td>
<td>3.5</td>
<td>3.08</td>
</tr>
<tr>
<td>14</td>
<td>90%</td>
<td>3.5</td>
<td>3.12</td>
</tr>
<tr>
<td>16</td>
<td>91%</td>
<td>3.3</td>
<td>3.00</td>
</tr>
<tr>
<td>18</td>
<td>92%</td>
<td>3.3</td>
<td>3.04</td>
</tr>
<tr>
<td>20</td>
<td>94%</td>
<td>2.7</td>
<td>2.54</td>
</tr>
</tbody>
</table>

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Management of ARDS: Impaired Oxygenation

Prone Positioning

Anterior

Atelectasis

Perfusion

Reduced Atelectasis

Perfusion

Anterior

Improved V/Q Mismatch
Management of ARDS: Impaired Oxygenation

Response to Prone Position

PaO2/FIO2 > 20 or PaO2 > 10mmHg

Management of ARDS: Impaired Oxygenation

Atelectasis

Anterior Inhaled Vasodilator

Perfusion

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Management of ARDS: Impaired Oxygenation

Inhaled Nitric Oxide
- Reverses Hypoxemic Vasoconstriction
- Improves V/Q Mismatch

Graph:
- PaO2/FIO2 Ratio
- Baseline: 150
- Nitric Oxide 18ppm: 220
- p<0.01

Rossaint et al. *NEJM* 1993C
Management of ARDS: Impaired Oxygenation

Intratracheal Surfactant: Surfactant is Decreased/Inhibited in ARDS

ARDS (within 48-72º)

Surfactant + Protein C (n=224)

Placebo (n=224)

4 doses over 24 hours

PaO₂/FI0₂ Mortality

Spragg et al. NEJM 2004
Management of ARDS: Impaired Oxygenation

Surfactant Treated Patients Demonstrated Improved P/F Ratio

\[ \text{PaO}_2/\text{FiO}_2 = \begin{cases} \text{Surfactant Group} & \text{P} < 0.001, \text{P} = 0.02, \text{P} = 0.03, \text{P} = 0.05 \\ \text{Control Group} & \end{cases} \]

Spragg et al. NEJM 2004
Surfactant Treated Patients Demonstrated No Improvement In Ventilator Free Days

Management of ARDS: Impaired Oxygenation

Spragg et al. NEJM 2004
Case Presentation:

Because of High FiO2 Requirements (80%), Our Patient Underwent a Best PEEP Titration. Her Ventilator Settings Are Now:

Rate-35, Tidal Volume-350 ml (5 cc/kg), PEEP-14 cmH2O.

Her FiO2 Requirements Are at 60%.

Her Airway Pressure on Her Current Tidal Volume Remains at 26 cmH2O.

Her ABG is: pH-7.33, pCO2-48, pO2-55, O2 sat-88%
Management of ARDS:

- Impaired Oxygenation:
  - V/Q Mismatch
  - Shunting

- Reduced Compliance

- Impaired Oxygenation:
  - V/Q Mismatch
  - Shunting

- High Mortality

Mechanical Ventilation
Trend in ARDS Mortality Rate

ARDS Fatality Rates

Fatality Rate (%) vs. Year


Fatality Rate (%): 30, 35, 40, 45, 50, 55, 60, 65, 70

Hudson et al. JAMA 1995
Case Presentation:

Now that Our Patient has Stabilized on the Ventilator, Are There Any Treatments that Can Improve Her Likelihood of Survival?
## Risk Factors for ARDS Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Pulmonary Organ System Dysfunction</td>
<td>8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>5.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Severity of ARDS as Measured by P/F ratio Has Minimal Impact on Survival

Matthay et al. *Am J Respir Crit Care Med* 1995
Multi-Organ Failure in ARDS Network Trial

Median Organ Failure Free Days

- Renal
- Coagulation
- Cardio
- Hepatic
- CNS
- Pulmonary

Time (days)

- 12cc/kg
- 6cc/kg

* P < 0.05

ARDSnet NEJM 2000
### Drug Treatment Trials to Reduce ARDS Mortality

<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.\textsuperscript{116}</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.\textsuperscript{27}</td>
</tr>
<tr>
<td>Alprostadil</td>
<td>1989</td>
<td>Phase 3</td>
<td>100</td>
<td>No benefit</td>
<td>Bouc et al.\textsuperscript{126}</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abraham et al.\textsuperscript{128}</td>
</tr>
<tr>
<td>Liposomal</td>
<td>1999</td>
<td>Phase 3</td>
<td>350</td>
<td>Stopped for lack of efficacy</td>
<td>Anzueto et al.\textsuperscript{116}</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></td>
</tr>
<tr>
<td>Glucocorticoids during the fibrosing-alveolitis phase</td>
<td>1998</td>
<td>Phase 3</td>
<td>34</td>
<td>Decreased mortality, but study was small</td>
<td>Meduri et al.\textsuperscript{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.\textsuperscript{129}</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.\textsuperscript{129}</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>2000</td>
<td>Phase 2</td>
<td>234</td>
<td>No benefit</td>
<td>NIE Acute Respiratory Distress Syndrome Network\textsuperscript{132*}</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 C; unpublished data</td>
</tr>
<tr>
<td>Lipofylline</td>
<td>1999</td>
<td>Phase 2</td>
<td>235</td>
<td>Stopped for lack of efficacy</td>
<td>Unpublished data</td>
</tr>
</tbody>
</table>
Drug Therapy to Reduce ARDS Mortality

Exudative Phase (7 Days) ↔ Proliferative Phase (14 Days) ↔ Fibrotic Phase (21 Days)

Glucocorticoids

Inflammation
Drug Therapy to Reduce ARDS Mortality

Glucocorticoids: Inflammation Drives Fibroproliferative Phase of ARDS

ARDS
(≥7 days)

Glucocorticoids
(n=89)

Placebo
(n=91)

60 Days

PaO₂/FI O₂
Organ Dysfunction
Mortality

Steroid Dosing:
2 mg/kg x 1 dose
then 0.5 mg/kg every 6 hrs x 14 days
then 0.5 mg/kg every 12 hrs x 7 days
then taper.

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### Treatment to Reduce ARDS Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Steroid</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator Free Days at Day 28</td>
<td>6.8 ± 8.5</td>
<td>11.2 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU Free Days at Day 28</td>
<td>6.2 ± 7.8</td>
<td>8.9 ± 8.2</td>
<td>0.02</td>
</tr>
<tr>
<td>60 Day Mortality (%)</td>
<td>28.6</td>
<td>29.2</td>
<td>1.0</td>
</tr>
<tr>
<td>60 day Mortality From Time of ARDS Onset (7-13 days)</td>
<td>36</td>
<td>27</td>
<td>.26</td>
</tr>
<tr>
<td>60 day Mortality From Time of ARDS Onset (After Day 13)</td>
<td>8</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Source: Undetermined
Summary/ Key Points

ARDS is Diagnosed by Clinical Parameters:
- Acute Onset in Appropriate Setting
- Bilateral Infiltrates
- Reduced Oxygenation
- No Evidence of CHF

Definition Lacks Specificity. Differential Diagnosis Includes:
- Congestive Heart Failure
- Alveolar Hemorrhage
- Pneumonia
- Aspiration

Pathophysiology Includes:
- Systemic Inflammation
- Injury to the Alveolar Membrane
- Alveolar Flooding with Plasma Fluid
- Inactivation of Surfactant

Respiratory Distress
↓ Resp. Rate
Hypoxemia
↓ Compliance
Bilateral Infiltrates
Summary/ Key Points

Management Problems:
- Decreased Compliance
- Refractory Hypoxemia
- High Mortality

Strategies to Manage:
- Decreased Compliance
- Refractory Hypoxemia
- High Mortality

Risk Factors for Mortality:
- Multi-organ Failure
- Underlying Cause of ARDS
- Not Degree of Hypoxemia

Low Tidal Volume Ventilation
Permissive Hypercapnea
Best PEEP Curve
Prone Positioning
Inhaled NO2
Additional Source Information
for more information see: http://open.umich.edu/wiki/CitationPolicy

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Slide 16: Thomas Sisson
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