Acute Respiratory Distress Syndrome (ARDS)

What is “Acute Respiratory Distress Syndrome”?

- Acute hypoxemic respiratory failure with diffuse, inflammatory lung injury leading to pulmonary vascular permeability edema
- Clinically, hallmark features are those of hypoxemia, bilateral radiographic opacities, with
  - increased shunt fraction
  - increased physiological dead space
  - and decreased lung compliance
- Pathologically, diffuse alveolar damage is most commonly noted

ARDS Definitions.. Then.. And Now..

<table>
<thead>
<tr>
<th>AECC 1994 Definition</th>
<th>Berlin 2012 Definition</th>
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<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Onset- Clarified * within 1 week of known clinical insult or new symptoms</td>
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<tr>
<td><strong>Chest Imaging</strong></td>
<td>Bilateral opacities not fully explained by lobar consolidation, collapse or nodules</td>
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<tr>
<td><strong>Origin of Edema</strong></td>
<td>Respiratory Failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g echocardiography) to exclude hydrostatic edema if no risk factor present</td>
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<tr>
<td><strong>Oxygenation</strong></td>
<td><strong>Mild</strong></td>
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<tr>
<td>ARDS → PaO₂/FiO₂ ratio less than 200</td>
<td>200&lt;PaO₂/FiO₂ ≤ 300</td>
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<tr>
<td>Acute Lung Injury → PaO₂/FiO₂ ratio less than 300</td>
<td>CPAP or PEEP=⇒ 5cms H₂O</td>
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</table>
ARDS is fairly common and has high mortality
- 10% of all ICU patients and 23.4% of all patients with Mechanical Ventilation in ICU
- Overall hospital mortality - 40%
- ARDS Period Prevalence: Mild - 30%, Moderate - 46.6% and Severe - 23.4% and hospital mortality progressively increases with severity to 46%
- ARDS can develop under our watch!

Why is this important for us?

How does ARDS develop?
- Direct Lung Injury
  - Pneumonia
  - Aspiration
  - Pulmonary contusion
  - Near-drowning
  - Inhalation injury
  - Reperfusion injury
  - Amniotic fluid and fat embolism
- Indirect Lung Injury
  - Sepsis
  - Massive trauma
  - Multiple transfusions
  - Acute pancreatitis

ARDS develops while in the hospital

First Hit, Second Hit Hypothesis

First Risk Modifiers
- Chronic Alcohol Use
- Smoking Status
- Low Albumin
- Acidosis
- Obesity
- Silent Aspiration

Second Risk Modifiers
- Ventilator Induced Lung Injury
- RBC, Platelets and FFP transfusions
- Fluid Overload
- FiO2 use

Pathophysiological Changes and What They Mean...

Acute Exudative Phase (Minutes to hours)
- Pulmonary endothelial and alveolar epithelial injury
- Increased permeability edema
- Surfactant dysfunction
- Hypoxemia
- Increased dead space
- Platelet and procoagulant injuries
- Acute hypoxemia, increased dead space
- Venous admixture (V/Q mismatch)

Chronic Proliferative Phase (5 - 7 days)
- Maladaptive repair with mesenchymal cells and proliferative fibroblasts
- Acute hypoxemia, increased dead space
- Venous admixture (V/Q mismatch)
- Pulmonary hypertension
- Weaning and Ventilator Liberation

Recovery
- Alveolar edema and proteins are cleared, endothelial and epithelial injury repaired
- Acute hypoxemia, increased dead space
- Venous admixture (V/Q mismatch)
- Pulmonary hypertension
- Weaning and Ventilator Liberation
High Dead Space 

Alveolar Collapse 

Low PaO₂ due to reduced Cardiac Output (Shock) 

High Pulmonary artery pressure (Pulm HTN) 

Refractory Hypoxemia 

Low Shunt 

What can you do? What should you do? 
First Step- RECOGNIZE ARDS! Start Lung Protective Ventilation! 

• Lung Safe - Only 60% patients with ARDS were diagnosed on day of admission 
• The continuum of lung injury, like sepsis time probably matters here too! 

What can you do? What should you do? 

• VT: How to set a safe VT? Is a low VT good for all? 
• PEEP: How should the appropriate PEEP be determined? 
• Plateau pressures: keep limited, <30cms, what else do we need to know 
• FiO₂: Yes, we know too much is bad, but how do we lower it when the patient needs oxygen? 

Lung Protective Ventilation 

Low Tidal Volume = Survival 

Low (6ml/kg IBW) vs traditional tidal volume (12kg/IBW) in ARDS 

➢ 6cc/kg tidal volume group had 8.8% absolute mortality benefit (NNT=12) 
➢ Proportion alive and off ventilator improved 
➢ Non-pulmonary organ failure improved 
➢ Markers of inflammation reduced 

Eligible—lower vs higher Vt in patients without ARDS at onset of MV

20 studies, 2822 patients
Randomized studies—15, non-randomized studies—5
Decrease in ALI (RR: 0.33; 95% CI: 0.23 to 0.47; NNT: 11)
Mortality (RR, 0.64; 95% CI, 0.46 to 0.89; NNT, 23)

Non-volume controlled mode is the most important barrier to implementation of Lung Protective Mechanical Ventilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI), P</th>
<th>Adjusted OR (95% CI), P</th>
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</thead>
<tbody>
<tr>
<td>Age, per SD (16 y)</td>
<td>1.14 (1.02-1.28), 0.021</td>
<td>1.18 (1.02-1.38), 0.028</td>
</tr>
<tr>
<td>Sex, female</td>
<td>2.03 (1.61-2.56), 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Race, white vs nonwhite</td>
<td>1.26 (0.99-1.63), 0.090</td>
<td>1.40 (1.05-1.88), 0.023</td>
</tr>
<tr>
<td>BMI per SD (7.3 kg/m²)</td>
<td>1.12 (0.95-1.28), 0.700</td>
<td>NS</td>
</tr>
<tr>
<td>Height, per SD (10 cm)</td>
<td>0.96 (0.92-1.01), 0.001</td>
<td>0.95 (0.94-0.98), 0.001</td>
</tr>
<tr>
<td>Weight, per SD (22 kg)</td>
<td>0.96 (0.77-1.16), 0.755</td>
<td>0.96 (0.77-1.16), 0.755</td>
</tr>
<tr>
<td>SAPS II, per SD (14)</td>
<td>0.96 (0.77-1.16), 0.755</td>
<td>0.96 (0.77-1.16), 0.755</td>
</tr>
<tr>
<td>Direct lung injury</td>
<td>0.76 (0.58-0.99), 0.035</td>
<td>NS</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.80 (1.87-5.61), 0.055</td>
<td>NS</td>
</tr>
<tr>
<td>ARDS</td>
<td>0.84 (0.42-0.97), 0.065</td>
<td>NS</td>
</tr>
<tr>
<td>Radiographic lung injury-score per SD (0-5)</td>
<td>0.84 (0.74-0.99), 0.098</td>
<td>0.83 (0.79-0.86), 0.008</td>
</tr>
<tr>
<td>Non-volume-controlled mode</td>
<td>3.13 (2.03-4.77), 0.001</td>
<td>3.07 (1.76-5.37), 0.001</td>
</tr>
<tr>
<td>Serum bicarbonate per SD (5.5 mmol/L)</td>
<td>0.92 (0.82-1.03), 0.14</td>
<td>0.93 (0.87-0.99), 0.017</td>
</tr>
<tr>
<td>Duration of ICU stay before study enrollment per SD (2 d)</td>
<td>0.90 (0.60-1.31), 0.76</td>
<td>0.84 (0.73-0.98), 0.02</td>
</tr>
</tbody>
</table>

No difference in mortality

1. NEJM 2004;351:327-336
2. JAMA 2008;299:637-245
3. JAMA 2008;299:646-655
What else helps to set PEEP?

Think About...

**Driving Pressure as a Ventilator Variable**

Strong association between ΔP and survival even lung-protective ventilator settings (relative risk of death, 1.36; CI 95%, 1.17 to 1.58; P<0.001)

**Transpulmonary Pressure**

A ventilator strategy using esophageal pressures to estimate the transpulmonary pressure significantly improves oxygenation and compliance

How to set Optimal PEEP

- Recruitment potential - most important
- PEEP of zero (ZEEP) harmful in ARDS
- Usually 8-15 cm appropriate (up to 18 cms in studies), PEEP> 24 cms seldom required
- Driving Pressure: PEEP- Plateau pressure, aim for less than 15
- Transpulmonary pressure and chest wall mechanics play an important role
- Limiting factors- No recruitment, worsening hemodynamic compromise or hypotension

Plateau Pressure – End Inspiratory Alveolar Pressure

- Inspiratory pause of at least 0.5 sec needed to measure plateau pressure
- Surrogate for maximum lung distension, per ARDSnet Data: Suggestions to limit to 25-30cms
- Intra thoracic pressures can be high due extrinsic factors such as obesity, pleural effusion, abdominal distension etc..
- In these conditions, plateau pressure correlates poorly with the transpulmonary pressure
- If plat pressure> 30 cms then
  - Increase sedation, may require neuromuscular blockade
  - Drop TV to 4cms
  - May have to reduce PEEP by 2 cm decrements

Setting the Ventilator in ARDS for Lung Protective Ventilation

- Prefer Volume Control Mode
- $V_T = 6 \text{ ml/kg IBW}$
  - May adjust as low as 4 ml/kg IBW as needed or upto 8ml/kg IBW
- Set RR, Permissive Hypercapnia acceptable
  - Arterial pH as low as 7.20-7.15 due to hypercapnia may be accepted
- Set PEEP: ARDSnet PEEP-FiO₂ tables, Driving Pressure
Setting the Ventilator in ARDS for Lung Protective Ventilation

- Measure Plateau Pressure, aim to limit less than 30 cm H₂O
- Pay attention to patient size and chest wall
- Prevent patient ventilator dysynchrony
  - NMB, heavy sedation
- Adjust FiO₂ to target:
  - PaO₂ 55-80 mmHg
  - SpO₂ 88-95%

What change would you make on the ventilator next?

- 40yo with gram negative bacteremia
- On vasopressors
- Worsening oxygenation
- ABG pH:7.32
  - PaCO₂:33 PaO₂=55
- MV mode: A/C
- RR: 32 per min
- Tidal Volume: 500cc
  - (7 ml/kg)
- PEEP 6; FIO₂ 100%

What change would you make on the ventilator next?

- 65yo intubated for airway protection with drug overdose
- ABG pH:7.38
  - PaCO₂:44 PaO₂=110
- MV mode: A/C
- RR: 18 per min
- Tidal Volume: 600cc
  - (9 ml/kg)
- PEEP 6; FIO₂ 50%
What would you do next?

- 35 yo F, Day 2- post partum with acute onset dyspnea
- Ventilator settings:
  - FiO\textsubscript{2} 100%,
  - Peep 18 cms
  - TV: 320 (5cc/kg IBW)
  - RR 28,
  - Plateau pressure 28
  - PaO\textsubscript{2}/FiO\textsubscript{2} ratio : 57
  - ABG: pH=7.20, PaCO\textsubscript{2} = 63, PaO\textsubscript{2} = 57, bicarb: 21
  - Transthoracic Echo: Acute RV failure, LV preserved
  - Increasing vasopressor requirements

Source: MFMER

What next!

So you did all this, but the patient does not respond.

Matthew Exline, MD
Associate Professor - Clinical
Department of Internal Medicine
Division of Pulmonary, Allergy, Critical Care
and Sleep Medicine
The Ohio State University Wexner Medical Center

Life Saving Therapy In ARDS

- ARDS care is NOT just supportive care
- There are active measures we can take today to save lives
- We’ve got to look for the patients that we can help
  - They are usually NOT the hardest to ventilate
- What can we do?

ARDS Care 2018
**Helps Oxygenation / Ventilation**
- High PEEP
- Diuretics
- Inhaled Vasodilators

**Diuresis**

**A Dry Lung is a Happy Lung**

- Starling’s Law and Pulmonary Edema
  - $Q_f = K_{fc} \left[ (P_{mv} - P_i) - (s_d)(T_{mv} - T_i) \right]$
  - Where
    - $Q_f$ = net fluid filtration
    - $K_{fc}$ = capillary permeability coefficient
    - $P$ = hydrostatic pressure
    - $TT$ = osmotic pressure
    - $mv$ = microvascular
    - $i$ = interstitial
    - $s_d$ = average osmotic coefficient

- Increased in ARDS due to leaky capillaries
  - $Q_f = K_{fc} \left[ (P_{mv} - P_i) - (s_d)(T_{mv} - T_i) \right]$

- Increased in ARDS due to volume overload
- Diuresis should help here

- 1001 patients with ARDS
- Randomized to “liberal” versus “conservative” fluid management
- Liberal targeted CVP 10-14mmHg
- Conservative CVP 4-8mmHg
**Diuresis to Get Off Vent**

- IF
  - No shock
  - Good urine output
  - "Wet" (CVP > 4)
  - DIURESIS
- Averaged 2.5 less days on vent

**Inhaled Vasodilators**

- Arginine → NO
- NO Synthase
- Endothelial Cell
- NO → Guanylyl Cyclase
- cGMP
- Smooth Muscle Cell
- Smooth Muscle Relaxation

**Mechanism Inhaled NO**

**Inhaled Vasodilators and ARDS**

- What has been shown:
  - Decreased Pulmonary Vascular Resistance (PVR)
  - Decreased Pulmonary Arterial Pressure (PAP)
  - Decreased Shunt Fraction and V/Q mismatch
  - Improved SaO₂

- What has not been shown:
  - Improved mortality
  - Sustained improvement in oxygenation
  - Increased time off vent
  - Decrease ICU or hospital days

Benzing et al., ’94; Rossaint, ’93
Improves Mortality

- Prone Ventilation
- Extracorporeal Membrane Oxygenation (ECMO)
- Airway Pressure Release Ventilation (APRV)
- Sedation Interruption
- Paralysis
- Low Tidal Volume

Which of These Saves Most Lives?
Number Needed to Treat (NNT)

- Low Tidal Volume NNT 10
- Paralysis NNT 9
- Sedation Interruption NNT 7
- APRV NNT 7*** (small study)
- ECMO NNT 5-8
- Prone Ventilation NNT 6

So You Want MORE Sedation Paralytics in ARDS

- Often used to improve compliance and reduce oxygen consumption
- In 340 patients with P/F ratio < 150
- Assigned to 48h of deep sedation (Ramsay 6) and either cisatracurium or placebo

Crude Mortality 90-day 31.6% vs 40.7%, adjusted HR 0.68
What About Sedation?

- Sedation is often necessary for ventilator compliance and patient comfort
- However, sedation should be considered a necessary evil
- Many studies have demonstrated sedation protocols improve outcomes, for example…

- 336 Patients compared between usual care and paired sedation interruption with spontaneous breathing trial
- 1-year mortality
  - 44% (intervention) v. 58% in control
  - NNT 7
- More self-extubations in intervention group, but reintubation rates the same

Do My Patients Want to Remember This?

- Patients without memories of the ICU were more likely to report lower health-related quality of life at 6-months post-ICU stay
- Patients with delusions, but no factual memory of the ICU had higher incidence of PTSD at 8 weeks

When the RT Talks Fancy!
Airway Pres Release (APRV)

- Ventilator mode where patient spends majority of the time at high PEEP with intermittent brief “release” times to allow for ventilation
- Patients are able to spontaneously breath while at high PEEP
- In theory, higher PEEP and spontaneous breathing facilitate open lung ventilation and lower sedation needs
Does APRV Work?

- No evidence it’s better (or worse)
- Danger with large transpulmonary pressure and large “release” volume
- In one small study, APRV patients had
  - More time off vent
  - Improved survival
  - Decreased sedation
- More work is needed to confirm role in ARDS and develop protocols

Extracorporeal Membrane Oxygenation (ECMO)

- 180 adults with severe ARDS
- Randomized to transfer to ECMO-capable center vs. Usual Care (at original hospital)
- 25% of “ECMO” patients did not placed on ECMO
- 6-month mortality
  - ECMO 37% versus Usual Care 53%
- ECMO can save lives, but
  - Need to be careful about patient selection
  - More important to be ECMO capable than get everyone on ECMO

Lancet 2009;374:1351

Easy, Cheap, Fast Proning in ARDS

- Proning
  - Laying patient on stomach for much of the day (> 16-hours)
- Improves pressure distribution
  - Less vent associated lung injury
- Improves secretion drainage
- Improves ventilation perfusion matching → ventilation and oxygenation improve

- 237 patients with ARDS
- P/F ratio 150 (moderate to severe)
  - e.g. PaO₂ of 74mmHg on 50% FiO₂
- Proned AT LEAST 16-hours a day
- Mortality 23.6% vs. 41%
**Proning for ARDS Not for Rescue Anymore**

- Proning is FREE!
- Proning can be done safely, just takes coordination with nursing, physicians, and respiratory therapists
- NNT for proning is 6
- Proning is not uncomfortable

**What’s the Future?**

- Paralysis (again) - ROSE
- Vitamin D - VIOLET
- Fluids (again) – CLOVERS
- Non-PETAL Network Studies
  - Vitamin C for Septic ARDS
  - Mesenchymal Stem Cell Infusions

**ARDS LIVE SAVING THERAPIES**

<table>
<thead>
<tr>
<th>What Buys Us Time</th>
<th>What Saves Lives!</th>
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<tr>
<td>PEEP</td>
<td>Low Tidal Volume</td>
</tr>
<tr>
<td>Diuresis</td>
<td>Minimize Sedation</td>
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<tr>
<td>Inhaled vasodilators</td>
<td>Paralytics</td>
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<tr>
<td></td>
<td>Prone Ventilation</td>
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<tr>
<td></td>
<td>ECMO</td>
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<td></td>
<td>APRV (maybe)</td>
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