ARDS/ALI: Unlocking The Seven Key Care Components for Successful Outcomes

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Disclosures

– Lilly Speaker Bureau
– Merck Speakers Bureau
– Sage Products Speaker Bureau & Consultant
– Hill-Rom Speaker Bureau & Consultant
Presentation Overview

- Defining Acute Lung Injury/ARDS
  - Links with the Systematic Inflammatory Response Syndrome
  - Incidence & mortality
- Pathophysiologic derangements
- Clinical signs & symptoms
- Supportive care: The 6 P’s of therapy
  - Prevention, PEEP, Pipes, Pump, Paralysis & Positioning
- Future therapies

Acute Lung Injury/ARDS: A Continuum

Normal Lung    Acute Lung Injury    ARDS

Direct or Indirect Injury
Definition…Acute Lung Injury

- **Timing** - Acute Onset
- **Oxygenation** - PaO$_2$ / FiO$_2$ < 300 regardless of PEEP levels
- **Chest x-ray** - Bilateral infiltrates seen on frontal chest x-ray
- **PCWP** - < 18 mmHg and/or no clinical evidence of left atrial hypertension


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**PaO$_2$/FiO$_2$ Ratio**

- User friendly tool
- Crude assessment of the severity of lung injury
- Used in the definition of ALI/ARDS
  - ALI: < 300 regardless of PEEP
  - ARDS: < 200 regardless of PEEP

© Vollman 2001
**Definition...Acute Lung Injury**

- **Timing**: Acute Onset
  - **Oxygenation**: \( \text{PaO}_2 / \text{FiO}_2 < 300 \) regardless of PEEP levels
  - **Chest x-ray**: Bilateral infiltrates seen on frontal chest x-ray
  - **PCWP**: \(< 18 \text{ mmHg} \) and/or no clinical evidence of left atrial hypertension


**Acute Respiratory Distress Syndrome**

- **Timing**: Acute Onset
  - **Oxygenation**: \( \text{PaO}_2 / \text{FiO}_2 < 200 \) regardless of PEEP levels
  - **Chest x-ray**: Bilateral infiltrates seen on frontal chest x-ray
  - **PCWP**: \(< 18 \text{ mmHg} \) and/or no clinical evidence of left atrial hypertension

_Revision Required_
Early Acute Lung Injury (EALI)  
(Can We Predict Progression?)

- 1935 screened patients with abnormal CXRs
- 100 patients enrolled with bilateral opacities present < 7 days and not due exclusively to LAH
- 33/100 progressed to ALI requiring MV (33%)
- Mean time to progression 22 hours
- Progression associated with:
  - Immunosuppression (p=0.07)
  - Modified rapid emergency medicine score (p=0.07)
  - SIRS
  - Initial O2 requirement > 2/L/Min (p=0.002)
- Clinical Dx of EALI: bilateral opacities, absence of isolated LAH, need for > 2/L min of O2 demonstrated 73% sensitive, 79% specific for progression to ALI


Epidemiology of ALI/ARDS

<table>
<thead>
<tr>
<th>Variables</th>
<th>US</th>
<th>Scandinavia</th>
<th>Australia</th>
<th>Europe</th>
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<tbody>
<tr>
<td><strong>ALI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>1,113</td>
<td>287</td>
<td>168</td>
<td>463</td>
</tr>
<tr>
<td>Incidence*</td>
<td>78.9</td>
<td>17.9</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>38.5</td>
<td>41.4</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td><strong>ARDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence*</td>
<td>58.7</td>
<td>13.5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>41.1</td>
<td>41.2</td>
<td>34</td>
<td>57.9</td>
</tr>
<tr>
<td>ARDS to ALI (ratio)</td>
<td>74</td>
<td>77</td>
<td>64</td>
<td>71</td>
</tr>
</tbody>
</table>

* Per 100,000 persons per year  
Rubenfeld GD et al. Chest 2007; 131:554-562
Mortality Rates for ALI/ARDS Over Time in RCT Studies

- ARDS Network Studies (RCT’s)
- 2451 Mechanical ventilated patients with ALI
- Crude mortality: 35% 1996-97
- 26% 2004-2005
- Adjusting for demographics & clinical covariates (trend p=.002)


Mortality Rates for ALI/ARDS Over Time in Observational & RCT Studies

- Prospective observational studies and RCT’s published during 1986-2006 that enrolled 50 or more patients
- Examined mortality trend before & after 1994
- 4966 studies: 89 met inclusion
- Pooled weighted mortality: 44.3% before 1994
- Pooled weighted mortality after 1994: 44%

ARDS
GOOD NEWS
85% WHO RECOVER HAVE NEAR NORMAL PULMONARY FUNCTION ONE YEAR LATER

Pathophysiologic Characteristics in ALI/ARDS

- A permeability defect described as a diffuse, non-uniform injury to the alveolar epithelium and alveolar capillary membrane (mediator/biotrauma & ventilator induced)
- Direct injury to pulmonary circulation (mediator/biotrauma & ventilator induced)
- Defect in the body’s ability to transport and utilize O₂ at tissue level

Gajic O et al. Crit Care. Online; April 26th, 2005
Biotrauma
Ventilator Induced Lung Injury: Parenchymal Injury

Known or Suspected Factors:
• Peak lung volume > TLC seen with Pplat >30cmH₂O
• Lung volume < the alveolar collapse point
• High rate/frequency of lung inflation
• High FiO₂

Wet Lung

• Collapsed alveoli and compression atelectasis
• Pooled airway fluid
• Inactivation and/or depletion of surfactant
Basilar Atelectasis

Pulmonary Vascular Injury

<table>
<thead>
<tr>
<th>Cause</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress fractures of capillaries</td>
<td>Leaky membranes</td>
</tr>
<tr>
<td>Unregulated vasoconstriction (mediators)</td>
<td>Increased PAP &amp; PVR</td>
</tr>
<tr>
<td>Vascular clogging/obstruction (micro emboli)</td>
<td>Pulmonary hypertension/Right ventricular dysfunction</td>
</tr>
</tbody>
</table>
**Pulmonary Hypertension**

Increase right ventricular work  
↓  
Increase right ventricular size  
↓  
Right ventricular shift  
↓  
Impedes left ventricle size  
↓  
Decrease stroke volume  
↓  
Decrease cardiac output  
↓  
Decrease Oxygen delivery

**ARDS**  
↓  
Pansystemic microvascular injury  
↓  
Increased permeability of the peripheral circulation  
↓  
Edema formation  
↓  
O₂ extraction  
↓  
O₂ delivery  
↓  
Cellular anaerobic metabolism  
↓  
MODS  
↓  
Biochemical mediators PMN's  
↓  
Endothelial injury of the GI tract  
↓  
Systemic translocation of bacteria  
↓  
Delivery of endotoxin to hepatic macrophages  
↓  
Export of cytokines & mediators from the liver  
↓  
MODS
Clinical Manifestations

- Refractory hypoxemia
- Pulmonary shunting
- Pulmonary hypertension
- Other organ system failures
- Decreased lung compliance
- Diffuse alveolar and interstitial infiltrates
<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
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</thead>
<tbody>
<tr>
<td>➢ Refractory Hypoxemia</td>
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<tr>
<td>➢ Pulmonary Shunting</td>
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<td>• Other organ system failures</td>
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<tr>
<td>• Decreased lung compliance</td>
</tr>
<tr>
<td>• Diffuse alveolar and interstitial infiltrates</td>
</tr>
</tbody>
</table>
Impact of Organ Failure With ARDS

- No organ failure
- Failure of 1 organ
- Failure of 2 organs
- Failure of ≥2 organs

Log rank test p value <0.001

Dorinsky & Gadek, Chest, 2007;132:829-835

Ware LB, Matthay MA. N Engl J Med, 2000;342:1334
ARDS Treatment Principles

- Prevent further injury
- Maintain adequate pulmonary oxygenation
- Optimize oxygen delivery
The Seven P’s of ARDS Treatment

- PREVENTION
- PEEP
- PUMP
- PIPES
- PARALYSIS
- POSITION
- PROTEIN

Prevention
PREVENTING THE INVASION

- Handwashing
- Line care
- Oral care
- HOB

Ventilator Associated Pneumonia Risk Factor Categories

- Factors that increase bacterial burden or colonization
- Factors that increase risk of aspiration
Preventing VAP

- Comprehensive oral care
- Positioning/rotational & HOB
- Early enteral feeding/stress ulcer prophylaxis
- Reduce frequency of changing ventilator circuits
- MDI’s versus nebulizers, no routine use of saline
- Handwashing
- Weaning protocol
- Sedation protocol around the clock

Vollman KM. Crit Care Nurs Clin N Am, 2006; 18:453-467

PEEP

(Positive End Expiratory Pressure)
Strategies for Ventilating the ARDS Lung: Protect From Injury

- Oxygen exposure
- Pressure (Barotrauma)
- Volume (Volutrauma & Biotrauma)
- Shear forces (Reopening & closing of alveoli) (Atelectrauma & Biotrauma)

ARDS Network
ALI/ARDS Ventilator Study

Methodology:
- Inclusion criteria: p/f ratio < 300, bilateral infiltrates, no cardiac cause, receiving mechanical ventilation
- Outcomes: mortality/VFD
- 841 patients randomized
- 12 ml/kg TV group – Plat < 50 cm H₂O
- 6 ml/kg TV group - Plat < 30 cm H₂O
- TV calculated with Predicted Body Weight

ARDS Network
ALI/ARDS Ventilator Study

Results:

- PEEP: no difference in average amount used
- Mortality: 31% (6 ml/kg TV) vs. 40% (12 ml/kg TV) p=0.007
- VFD: 12+ 11 vs. 10+11 (p=0.007)
- Greater organ failure free days in protective group
- Reduction in IL-6 levels by day 3
- Difficulty with agitation/high rates in the 6 ml/kg group

No difference in supportive care requirements: vasopressors, fluids, diuretics, sedation (Cheng IW et al. Crit Care Med, 2005;33:63-70)


Is the Research Used?

- Physician: < 40% use tidal volumes < 7.0 ml/kg for patients who meet the ALI/ARDS criteria
  - Reason for Use: Lower PaO2 & Lower static compliance
- Nursing (49%) & Respiratory (44%) Survey of Reasons for Low Use: Median use 20 patients per respondent
  - Barriers to Initiation
    • MD willingness to relinquish control of vent
    • MD recognition of ALI/ARDS
    • MD perception of patient contraindications
  - Barriers to Continuation
    • Patient discomfort, tachypnea
    • Hypercapnia/acidosis

Kalhan R et al Crit Care Med, 2006;34:300-306
**Low Tidal Volume, Recruitment Maneuvers & High PEEP for ARDS/ALI**

**Methodology**
- Randomized controlled trial, concealed allocation & blinded analysis
- August 2000 to March 2006
- 30 ICU’s in Canada, Australia and Saudi Arabia
- 983 patients with ALI with P/F ratio not exceeding 250
- Control: target tidal volumes of 6ml/kg of PBW, Plateau pressure < 30 cm H2O & conventional levels of PEEP (n=508)
- Experimental: target tidal volumes of 6ml/kg of PBW, plateau pressures < 40 cm of H2O, recruitment maneuvers & higher PEEP (n=475)


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**Low Tidal Volume, Recruitment Maneuvers & High PEEP for ARDS/ALI**

**Results**
- 85% met criteria for ARDS
- Tidal volumes similar in both groups
- PEEP 14.6 (SD 3.4) vs. 9.8 (SD 2.7) first 72 hrs p<.001
- All cause mortality: 36.4% vs. 40.4% p = .19
- Barotrauma: 11.2% vs. 9.1% p = .33
- Experimental group:
  - Lower rates of refractory hypoxemia (4.6% vs. 10.2% p = .01)
  - Death with refractory hypoxemia (4.2% vs. 8.9% p = .03)
  - Previously define rescue therapies (5.1% vs. 9.3% p = .045)

Lung Protective Ventilation: EBR

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Protective nN</th>
<th>Conventional nN</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio 95% CI</th>
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<tr>
<td>Amato 1999</td>
<td>1579</td>
<td>1704</td>
<td></td>
<td>6.7 %</td>
<td>0.63 [0.39, 1.07]</td>
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<tr>
<td>Broschard 1998</td>
<td>3738</td>
<td>2258</td>
<td></td>
<td>7.9 %</td>
<td>1.23 [0.80, 1.91]</td>
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<tr>
<td>Stewart 1998</td>
<td>3060</td>
<td>2860</td>
<td></td>
<td>10.1 %</td>
<td>1.07 [0.74, 1.55]</td>
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<tr>
<td>Brower 1999</td>
<td>1326</td>
<td>1326</td>
<td></td>
<td>4.3 %</td>
<td>1.08 [0.62, 1.91]</td>
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<tr>
<td>ARDS Network 2000</td>
<td>13442</td>
<td>17842</td>
<td></td>
<td>61.5 %</td>
<td>0.70 [0.60, 0.93]</td>
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<tr>
<td>Vila 2004</td>
<td>17750</td>
<td>25465</td>
<td></td>
<td>9.5 %</td>
<td>0.64 [0.53, 0.83]</td>
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<tr>
<td>Total (95% CI)</td>
<td>655</td>
<td>6412</td>
<td>100.0 %</td>
<td>0.83 [0.72, 0.95]</td>
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</table>

Advantage to Lung Protective Strategy at 28 days & Hospital Discharge for TV < 7ml/kg & Plateau Pressure < 31cm H\text{\textsubscript{2}}O


Plateau Pressure May Serve As a Strong Prognostic Indicator

- Examine pre-enrollment data from 2451 patients enrolled in 6 trials (1996-2005) to look at V\textsubscript{t} over time
- Used logistic regression to see if pre-enrollment tidal volume or plateau pressures affected mortality
- Results
  - Median Vt decrease from 10.3 ml/kg PBW during trial to 7.3 ml/kg post trial; pre-enrollment VT no impact on mortality
  - 1.17x higher odds of death when pre-enrollment Pplat for ↑ from 15cm, 1.37x when ↑ from 20cm, 1.87x ↑ from 30 cm H\text{\textsubscript{2}}O

Checkley W, et al. AJRCCM, 2008 in press
Recruitment Strategies

- Optimal PEEP
- 30-40cm of CPAP for 30 seconds
- Prone positioning

*Contraindications: severe bronchospasm, bullous emphysema, untreated pneumothorax, unilateral lung dx, hemodynamic instability, unstable ICP

Cochrane Systematic Review: 7 trial met criteria for inclusion (1170 patients). Results showed no improvement with use of recruitment maneuver with 28 day mortality, risk of barotrauma, blood pressure but did increase oxygenation for short time periods

(Hodgson C et al. Cochrane Database of Systematic Reviews, 2009;2)

Pressure-Volume Curve
High Versus Low PEEP Study

Methodology

- 549 patients with ALI/ARDS
- Mechanical ventilation with low or high PEEP set according to predetermined tables of PEEP levels & FiO2 levels
- Tidal volume: 6/mL per kg of IBW
- At 171 patient enrollment/changed protocol because PEEP amounts were to similar between groups
- Measured: 28 mortality, VFD


High Versus Low PEEP Study

Results

- Trial stopped based on futility rule
- Group differences at baseline; High PEEP group; significantly older & lower PaO2/FiO2 ratio
- Mean PEEP day 1-4*
  - Low PEEP; 8.3 ± 3.2
  - High PEEP; 13.2 ± 3.5
- Mortality; Low PEEP= 27.5% (after adjustment)
  High PEEP= 25.1% (after adjustment)

EBR & Meta-analysis: High Peep vs. Low PEEP

- 6 trials, 2484 patients
- 102 critical care units worldwide
- 1233 (high PEEP: $\geq 10\text{cm H}_2\text{O}$ on Day 1, average $15\text{cm H}_2\text{O}$)
- 1251 (low PEEP: $< 10\text{cm H}_2\text{O}$ on day 1, average $8\text{cm H}_2\text{O}$)
- 3 studies also compared low tidal volume ventilation versus high tidal volume

EBR & Meta-analysis: Barotrauma with High PEEP vs. Low PEEP


PEEP Alone

- Brower et al
- Meade et al
- Mercat et al
- Combined (random)

Risk of Harm:
NNT=75
P= 0.25

Pressure Control

- Inspiration is terminated after a present pressure is obtained
- Tidal volumes vary making it difficult to control

Results:
- Lung protective strategy: controlled pressures & tidal volumes vary
- Recruitment of collapse alveoli
- May improve mortality but studies small and volume control group not ventilated with < 6 ml/kg

Esteban A et al Chest, 2000;117:1690-1696
For the Spanish Lung Failure Collaborative Group
Mechanical Ventilation Wean Protocol for Acute Lung Injury (ALI)/ARDS

An automatic weaning protocol should be in place and mechanically ventilated patients should undergo assessment of readiness to wean & spontaneous breathing trial when they satisfy the 2-step process:

- **Readiness to Wean:** Arousable, Low ventilatory and end expiratory pressure requirements, No new potentially serious conditions, Hemodynamically stable without vasopressors, Requiring levels of FiO2 that could be delivered with a face mask or nasal cannula
- **Perform a Spontaneous Breathing Trial:** 30 to 120 minutes with assessment of vent pattern, gas exchange, hemodynamics & comfort

Endotracheal Suctioning for ALI/ARDS Patients

Goal: Prevent Derecruitment of the Lung
- Closed circuit endotracheal suctioning
- Pre-oxygenation
- If disconnection should occur, consider recruitment maneuver to re-establish open alveoli or recruitment maneuvers during suctioning
- < 10 seconds per pass & pressure < 400cm H₂O
“Non-Conventional” Ventilatory Strategies

• APRV
• Dual control
• HFOV
• ECMO

APRV: Airway Pressure Release Ventilation

• Time-triggered, pressure-limited, time cycled
• Pressure release mechanism allows spontaneous breathing during both inflation & deflation phases
• Results in longer inflation time
• Benefits:
  – Recruits more slowly
  – Raised mean airway pressure without increasing applied PEEP
  – Additional spontaneous effort during inflation may enhance recruit and cardiac filling
  – May be more tolerable
• No demonstrated outcome benefit when compared to ARDS network trial (small # of RCT with low # subjects)

Macintyre N. Semin Respir Crit Care Med 2006;7:396-403
Mlcak RP. J of Burn Care & Research, 2009;30:176-177
Dual Control within a Breath

- Volume-assured support
- Pressure augmentation
  - When breath is triggered, ventilator targets pressure support
  - Ventilator monitors delivered tidal volume
    - If delivered tidal volume = set tidal volume, the breath is a pressure support breath
    - If the tidal volume < set volume when the flow decreases to the set peak flow, flow will remain constant until the volume is delivered

Haas et al. Respir Care 1995;40:716

High Frequency Ventilation

- HFJV: frequency <150/min
- HFO: frequency >150/min to 1800/min
- HFO:
  - Ventilation achieves gas exchange by utilizing sub-dead space tidal volumes providing a less traumatic method of recruiting and stabilizing lung volumes
  - Constant mean airway pressure which allows maintenance of alveolar recruitment
  - May show better results in oxygenation when used with the prone position*

High Frequency Oscillation Trials

- Mostly Observational or Retrospective
- 2 Randomized trials
  - Derdak et al. (Am J Respir Crit Care Med 2002;166:801-808)
    - 148 patients
    - No benefit in mortality, trend at 30 & 90 days
    - Tidal volume 10ml/kg (conduct 1997-2000)
  - Bollen et al. (Crit Care 2005, 9:430-439)
    - Study terminated due to poor accrual
    - 1 adult/1 pediatric trial met criteria
    - Not enough evidence to demonstrate a morbidity or mortality benefit

Improved Oxygenation Without Benefit to Mortality

HFOV: NHLBI Acute Lung Injury SCCOR Grant

Phase II Trail Ongoing
CESAR Study: Conventional Ventilation Vs. ECMO

- Age 18-65 yrs, potential reversible ARDS were randomized to transfer to ECMO center or continue to receive conventional care at a tertiary center
- Excluded if vented for > 7 days
- 180 patients enrolled (90 each group)
- Study stopped early because of efficacy

Results
- 63% alive post ECMO without severe disability 6 months post treatment compared with 47% in the control group

\[ \text{NNT} = 6 \]


PIPPES & PUMP

Measures to Improve Oxygen Delivery
Measures to Improve $O_2$ Delivery

- Fluid Management
  - Colloid vs. Crystalloids
  - Dry vs. Wet

Colloid Versus Crystalloid

**Methodology**
- 6997 critically ill patients
- Randomized to receive 4% albumin or normal saline for intravascular resuscitation over a 28 days period
- Outcome measured: Death from any cause during the 28 days post randomization

Colloid Versus Crystalloid

Results
- Similar baseline characteristics
- 726 deaths in albumin group
- 729 deaths in normal saline group (p=0.87)
- Proportion of patients with new single & multiple organ failure were similar (p=0.85)
- No difference in #ICU days, # hospital days, # of days on vent or days of CRRT

ARDS Network: Fluid Management Strategies in ALI

Methodology

- Multicenter randomized trial
- 1000 patients
- Compared conservative and liberal fluid management using explicit protocols over a 7 day period (43 hrs after admission to ICU & 24 hours after establishment of ALI/ARDS)
- Primary endpoint: measure mortality at 60 days
- Secondary endpoints: VFD, OFD & lung physiology


Results

- Mortality:
  - Conservative: 25.5%
  - Liberal: 28.4% (95% CI, -2.6 to 8.4% p=0.30)
- Cumulative Fluid balance:
  - Conservative: -136 ± 491 ml
  - Liberal: 6992 ± 502 ml (p<0.0001)
- Conservative: ↑ VFD (14.6 ± 0.5 vs. 12.1 = 0.5 p >0.01)
  ↓ ICU days (13.4 + 0.4 vs. 11.2 = 0.4 p<0.001)

Review of Fluid Management: ARDS Network Patients

- Retrospective review
- 844 patients from the Low tidal volume study
- Fluid management was based on physician preference
- Measured: cumulative fluid balance during 1st four days compared to VFD, ICU free days, death during hospitalization

Results

- 683 patients averaged > 3.5 L in positive fluid balance
- 161 patients had a negative fluid balance
- Lower morality with negative balance 20% vs. 37% p=.001
- Greater VFD’s 15 vs. 10 days; p=.001
- ICU free days 13 vs. 9 days; p = .009

Timing of Fluid Administration is Key

- Start as early as possible the administration of volume
- Control the efficacy of volume expansion with predefined goal-oriented therapy
- More fluid early, less fluid later
- Careful with potential onset of adverse effects
PARALYSIS

Balancing Oxygen Supply and Demand
“OKAY, LET’S GET THOSE EYEBALLS MOVING!!”

O₂ Supply Debt
Activities That Increase VO$_2$

- Dressing change 10%
- Physical exam 20%
- Agitation 18%
- Bath 23%
- Chest X-ray 25%
- Suctioning 27%
- Increased work of breathing 40%
- Weigh on sling scale 36%
- Position change 31%
- Linen change – occupied bed 22%
- Chest physiotherapy 35%

Strategies to Optimize Patient’s Tolerance to Activities

- Space activities
- Monitor for signs of intolerance
- Pre/post hyperoxygenate
- Determine if the intervention is essential
- Control variables that increase consumption
  - Pain management
  - Agitation management
  - Partial temp regulation
  - Shivering
Appropriate Sedation: Impacting Ventilator Outcomes

- Around the clock sedation administered via a protocol based on evaluation of sedative levels with a reliable and valid tool shorten time on vent, ICU & hospital length of stay, need for a trach*
- Daily interruption of sedative drug infusions decreases the duration of mechanical ventilation and LOS in the ICU In the group that had daily interruption, the duration of mechanical ventilation was reduced by 33% (2.4 days) and ICU LOS was reduced by 35% (3.5 days).
- Sedation assessment tools not being used in 45% of cases reviewed by UHC on day 4 ventilation

Brook AD & Ahrens TS et al Crit Care Med, 1999;27:2609-2615
Jacobi j. Pharmacotherapy, 2005;25:1S-2S

Use of Sedatives, Opioids & Neuromuscular Blocking Agents in Patient with ALI/ARDS

- Retrospective analysis, used ALVEOLI trial data
- 549 patients with ALI/ARDS
- Analysis: impact of sedatives, opioids, neuromuscular blocking agents on duration of MV, time to weaning & mortality

Results:
- Sedatives & opioids used in > 80% of patients, similar in both groups
- Use of sedatives & opioids but not NMB was associated with longer times on the vent and increase time to achieve 2-hr SBT (p <.0001)
- No difference in use between low & high PEEP group

Arroliga AC, et a. CCM 2008;36:1083-1088
POSITION
Where Does The Prone Position Fit into A Mobility Program?

When the patient’s alveoli have been recruited through conventional means & the FiO2 remains in an unsafe range

The goal of prone positioning is to reduce the iatrogenic complications of mechanical ventilation

Goldhill DR et al. Amer J Crit Care, 2007;16:50-62
Summary

Supine:
- Marked reduction in lung volumes
- Alteration in lung mechanics (low compliance/high resistance)
- Compression atelectasis
- Moderate hypoxemia

Prone:
- Increased FRC & improved compliance
- Shifting of lung water & densities
- Increased oxygenation

Prone Positioning: 3 Multicenter RCT’s Completed

<table>
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<tr>
<th></th>
<th>Italy</th>
<th>Spain</th>
<th>France</th>
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<tbody>
<tr>
<td>SP/PP</td>
<td>152/152</td>
<td>60/76</td>
<td>378/413</td>
</tr>
<tr>
<td>PP hours/day</td>
<td>≥ 6</td>
<td>= 20</td>
<td>≥ 8</td>
</tr>
<tr>
<td>Patients</td>
<td>ALI</td>
<td>ARDS</td>
<td>ARF</td>
</tr>
<tr>
<td>(P/F ratio &lt; 300)</td>
<td></td>
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<td>(P/F ratio &lt; 300)</td>
</tr>
<tr>
<td>Primary End-Point</td>
<td>Mortality Day-10</td>
<td>Mortality ICU</td>
<td>Mortality Day-28</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>40% ↓30%</td>
<td>50% ↓30%</td>
<td>40% ↓30%</td>
</tr>
</tbody>
</table>

Limitations Of The Clinical Prospective Randomized Prone-supine Trials

- Power of the study
- Criteria for pronation
- Duration and frequency of pronations
- Ventilation tidal volumes high
- Ventilatory setting unmodified during pronation
- Mixed categories of patients
- Differences between centres
- Treatment of the etiologic agent uncertain !!

Courtesy of P Pelosi
Meta-analysis: Prone Positioning

- Systematic review: Review Literature up to February 2008
- 13 trial: 1559 patients
- Over all methodological quality good

Effect on Mortality (effect p=0.52. Heterogeneity $I^2 = 0\%$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Prone, n/N</th>
<th>Supine, n/N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term prone positioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost et al$^a$</td>
<td>5/6</td>
<td>4/8</td>
<td>0.81 (0.43-1.56)</td>
</tr>
<tr>
<td>Papazian et al$^a$</td>
<td>3/13</td>
<td>5/13</td>
<td>0.60 (0.38-2.01)</td>
</tr>
<tr>
<td>Density et al$^a$</td>
<td>4/13</td>
<td>4/13</td>
<td>0.77 (0.28-2.14)</td>
</tr>
<tr>
<td>Overall effect p = 0.32. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged prone positioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gueret et al$^b$</td>
<td>77/152</td>
<td>73/152</td>
<td>1.05 (0.84-1.32)</td>
</tr>
<tr>
<td>Gueret et al$^c$</td>
<td>134/413</td>
<td>139/378</td>
<td>1.03 (0.84-1.26)</td>
</tr>
<tr>
<td>Overall effect p = 0.68. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect p = 0.52. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sud S, et al. CMAJ, 2008;178(9):1153-61

Effect on PaO2/FiO2 ratio (effect p = 0.001. Heterogeneity $I^2 = 0\%$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Prone, n/N</th>
<th>Supine, n/N</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wathen et al$^{a,d}$</td>
<td>14/7</td>
<td>14/7</td>
<td>1.28 (1.15-3.42)</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wathen et al$^{a,d}$</td>
<td>11/6</td>
<td>11/6</td>
<td>1.28 (1.15-3.42)</td>
</tr>
<tr>
<td>Overall effect p = 0.001. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wathen et al$^{a,d}$</td>
<td>12/6</td>
<td>12/6</td>
<td>1.28 (1.15-3.42)</td>
</tr>
<tr>
<td>Overall effect p = 0.001. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wathen et al$^{a,d}$</td>
<td>8/5</td>
<td>8/5</td>
<td>1.28 (1.15-3.42)</td>
</tr>
<tr>
<td>Overall effect p = 0.001. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect on VAP (effect p=0.04. Heterogeneity $I^2 = 0\%$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Prone, n/N</th>
<th>Supine, n/N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buzer et al$^a$</td>
<td>2/12</td>
<td>4/9</td>
<td>0.38 (0.09-1.32)</td>
</tr>
<tr>
<td>Watabe et al$^b$</td>
<td>1/8</td>
<td>2/8</td>
<td>0.50 (0.06-4.92)</td>
</tr>
<tr>
<td>Gourin et al$^a$</td>
<td>85/413</td>
<td>91/378</td>
<td>0.85 (0.66-1.11)</td>
</tr>
<tr>
<td>Vogenesser et al$^a$</td>
<td>13/21</td>
<td>15/19</td>
<td>0.69 (0.48-1.00)</td>
</tr>
<tr>
<td>Mancio et al$^a$</td>
<td>14/76</td>
<td>9/60</td>
<td>1.23 (0.57-2.64)</td>
</tr>
<tr>
<td>Overall effect p = 0.04. Heterogeneity $I^2 = 0%$.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Effect on Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of trials (patients)</th>
<th>No. (%) of patients with adverse event</th>
<th>RR (95% CI)</th>
<th>p value</th>
<th>I², SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure ulcers</td>
<td>6 (604)</td>
<td>153/504 (30.4)</td>
<td>1.36 (1.07-1.71)</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>Endotracheal tube obstruction</td>
<td>5 (204)</td>
<td>3/204 (1.5)</td>
<td>1.32 (0.94-1.85)</td>
<td>0.14</td>
<td>13</td>
</tr>
<tr>
<td>Accidental extubation</td>
<td>8 (662)</td>
<td>44/662 (6.6)</td>
<td>0.88 (0.48-1.60)</td>
<td>0.67</td>
<td>0</td>
</tr>
<tr>
<td>Loss of central venous or arterial access</td>
<td>7 (526)</td>
<td>25/526 (4.8)</td>
<td>0.67 (0.31-1.54)</td>
<td>0.31</td>
<td>0</td>
</tr>
<tr>
<td>Thoracostomy tube dislodgement</td>
<td>6 (504)</td>
<td>7/504 (1.4)</td>
<td>6.00 (0.73-49.2)</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>6 (336)</td>
<td>16/336 (4.8)</td>
<td>0.93 (0.35-2.45)</td>
<td>0.44</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>5 (230)</td>
<td>0/230 (0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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Effect on Pressure Ulcers

(Effect p = 0.01. Heterogeneity I² = 0%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Prone, n/N</th>
<th>Supine, n/N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leal et al[1]</td>
<td>1/8</td>
<td>0/8</td>
<td>3.00 (1.14-4.42)</td>
</tr>
<tr>
<td>Gallie et al[2]</td>
<td>55/152</td>
<td>42/152</td>
<td>1.31 (0.84-2.03)</td>
</tr>
<tr>
<td>Bourn et al[3]</td>
<td>2/12</td>
<td>2/9</td>
<td>0.75 (0.13-4.36)</td>
</tr>
<tr>
<td>Cutlay et al[4]</td>
<td>10/51</td>
<td>8/50</td>
<td>1.23 (0.53-2.85)</td>
</tr>
<tr>
<td>Vigliarot et al[5]</td>
<td>19/21</td>
<td>12/19</td>
<td>1.43 (0.49-4.27)</td>
</tr>
<tr>
<td>Chan et al[6]</td>
<td>2/11</td>
<td>0/11</td>
<td>5.00 (0.22-93.35)</td>
</tr>
<tr>
<td>Overall</td>
<td>25/5</td>
<td>24/9</td>
<td>1.36 (0.07-1.77)</td>
</tr>
</tbody>
</table>

Favours prone Favours supine

0.15 0.50 1.00 2.00 4.00

RR (95% CI)

Sud S, et al. CMAJ, 2008;178(9):1153-61

Prone-Supine II:
The Effects of Prone Positioning for Patients Affected by ARDS

Phase III Trial Completed
Prone Positioning
Model 965 Specifications

Height Range: 36" - 48"
Overall Bed Length: 94"
Overall Bed Width: 29"
Diagram of the pancake method (top and bottom sheet) to turn a critically ill patient prone. (From Balas M.C. Crit Care Nurse, 2000;20(1):35.)
Vollman Prone Positioner

Protein
(Nutrition)

Meta-analysis on Enteral Nutrition: Does The Type of Feeding Make a Difference

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odd ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arruda et al</td>
<td>0.448</td>
<td>0.251</td>
<td>0.805</td>
<td>-1.77</td>
<td>.08</td>
</tr>
<tr>
<td>Bigler et al</td>
<td>0.205</td>
<td>0.125</td>
<td>0.352</td>
<td>-2.20</td>
<td>.028</td>
</tr>
<tr>
<td>Guzek et al</td>
<td>0.903</td>
<td>0.194</td>
<td>1.725</td>
<td>-1.06</td>
<td>.288</td>
</tr>
<tr>
<td>Final effect</td>
<td>0.104</td>
<td>0.041</td>
<td>0.378</td>
<td>-2.45</td>
<td>.015</td>
</tr>
</tbody>
</table>

Mortality: OR=0.40:95% CI=0.24-0.68;P=0.001

3 RCT’s (n=411) in patients with ALI/ARDS

Arruda AP, et al. CCM 2006;34:2325-2333
Meta-analysis on Enteral Nutrition: Does The Type of Feeding Make a Difference

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistic for each study</th>
<th>Note</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porta et al. 2005</td>
<td>0.053</td>
<td>0.028 0.043 0.041</td>
<td>-0.086</td>
</tr>
<tr>
<td>Senger et al. 2003</td>
<td>0.025</td>
<td>0.032 0.039 0.046</td>
<td>-0.076</td>
</tr>
<tr>
<td>Arruda et al. 2006</td>
<td>0.024</td>
<td>0.029 0.026 0.026 0.026</td>
<td>-0.071</td>
</tr>
<tr>
<td>Redefinition</td>
<td>0.026</td>
<td>0.026 0.026 0.026 0.026</td>
<td>-0.071</td>
</tr>
</tbody>
</table>

VFD: 4.9 days p< 0.0001

Reduction in New Organ Failure: p< 0.0001

Arruda AP, et al. CCM 2006;34:2325-2333

SSCM Nutritional Guidelines (2009)

- Targeted for ICU pts > 2 - 3 day LOS
- ARDS/severe ALI EN formula with anti-inflammatory lipid profile (Grade A)
- Nutritional therapy in form of EN should be initiated in patients unable to maintain volitional intake (Grade C)
- EN preferred route (Grade B), EN start 24-48hrs (Grade C), advance towards goal over next 48-72hrs (Grade E)
- EN withheld until unstable patient fully resuscitated (Grade E)
- Neither presence or absence of bowel sounds, or passage of flatus or stool required before initiation (Grade B)
- Either gastric or small bowel feeding acceptable. If at high risk feed via small bowel (Grade C)
- Hold for gastric residuals > 500 ml in absence of other signs of intolerance (Grade B)

Pharmacological Treatment

- The Unsuccessful Eighth “P” of ARDS Management

Pharmacological Management

- Modulation Therapies: Failed
  - Antioxidants
  - NSAIDS
  - Ketoconazole
  - IL-1 receptor antagonist
  - Neutrophil Elastase Inhibitor (Sivelestat)
  - Nitric oxide
  - Steroids
  - Surfactant
**Multicenter Surfactant Trial**


**Meta-analysis: Nitric Oxide Impact on Oxygenation & Mortality in ALI**

**Methodology:**
- 12 trials randomly/1237 patients met inclusion criteria
- Methodology criteria good

**Results:**
- No significant effect of NO on:
  - Hospital mortality
  - Duration of mechanical ventilation or VFD
  - Day 1, P/F ratio improved
  - No effect on MPAP
  - Significant risk of developing renal dysfunction

**Not Recommended for Routine Use in ALI**

ARDS Network: Steroids for Persistent ARDS

Methodology
- Multicenter, randomize controlled trial
- 180 patients with ARDS for ≥7 days to 28 days
- P/F ratio < 200 on study day entrance
- Measured mortality at 60 days, VFD & Organ failure free days, biochemical markers of inflammation, fibroproliferation & infectious complications

Results
- Mortality:
  - Steroid group: 29.2% (95% CI, 20.8 to 39.4%)
  - Placebo group: 28.6% (95% CI, 20.3% to 38.6%)
- Methylprednisolone associated with higher mortality among patients enrolled at least 14 days post onset
- Methylprednisolone increased the # VFD (14 vs. 23 days), ICU free days and Shock free days during the first 28 days

Meta-analysis: Steroids in ALI/ARDS

- 5 cohort studies (n=307)
- 4 RCT’s (n=341)
- Trend towards mortality reduction RCT p= 0.08
  - Cohort p= 0.06
  - Combined p=0.01
- Improvement in VFD, ICU LOS
- No increase in infection or major complications
- Recommend additional RCT for mortality effect with early use

Phase III: Partial Liquid Ventilation

Methodology
• 3-arm prospective, multicenter randomized controlled trial
• Comparing high and low dose PLV to conventional ventilation
• 311 patients
• Measured: MVFD, mortality & P/F ratio

Results
• Fewer VFD and a trend towards increased mortality

Kacmarck RM et al. Am J Respir Crit Care Med, 2006;173:882-889
The Future

- Bundling of Care
- New Ventilator modes?
- IVOX?
- Granulocyte Macrophage Colony-Stimulating Factor
- Beta-2 Adrenergic Agonists
- Biomarker: Urine Nitric Oxide
  - Modulation Therapies: Xigris (Activated Protein C)
The Vent Bundle & The 7 P’s

- Applying evidence-based practice
- 5 activities that when done 100% of the time has shown a reduction in
  - VAP
  - LOS
  - Time on Vent
  - Cost
- HOB 30°, DVT prophylaxis, PUD prophylaxis, Sedation vacation, Spontaneous breathing trial
  (added components in some areas of the countries
  (oral care & mobility)

The Future

- Bundling of Care
- New Ventilator modes ?
- IVOX ?
- Beta-2 Adrenergic Agonists
- Modulation Therapies: Xigris (Activated Protein C)
Beta-2 Adrenergic Agonists

- Potential Impact from animal & preclinical human studies
  - Reduce neutrophil sequestration & activation
  - Enhance alveolar fluid clearance & surfactant secretion
  - Modulate inflammatory & coagulation cascades
  - High dose salbutamol showed significantly more days alive and free of ALI*
  - Reduced lung water in 40 patients with ALI/ARDS**

Phase III ARDS Network Trial

Levitt JE & Matthay MA. Semin Respir Crit Care Med 2006;27:426-438
Manocha S et al. Crit Care 2006;10:R12

Activated Protein C in ARDS Patients

- Multicenter double blind placebo controlled study
- Enrolled patients with APACHE < 25 & no evidence of severe sepsis (similar to ADDRESS trial patients)
- Primary endpoint: VFD
- Study stopped because of lack of efficacy after 75 patients
- No difference in significant bleeding events

Long Term Outcomes

One-Year Outcomes In Survivors in ARDS

- 109 ARDS survivors evaluated at 3, 6 & 12 months post illness
- Survivors young (45 years), Long ICU LOS (median 25 days) and APACHE II > 23
- Loss of 18% Body wt at d/c from ICU
- Muscle wasting & fatigue were reasons for functional limitations
- Lung function & spirometric’s normal 6 months
- CO2 diffusion capacity low for full 12 months
- Absence of steroid use, absence of illness acquired during ICU stay & MODS had better functional status.

Self-Reported Symptoms of Depression & Memory Dysfunction in Survivors of ARDS

- 109 ARDS survivors over 4 years, 27 not included (death post hospitalization over a 4 year period, withdrew from study)
- 82 questionnaire sent, 71 Memory assessment returned, 68 Beck Depression Inventory returned
- Results:
  - ARDS survivors report a high prevalence of depressive symptoms (may hinder return to work)
  - Lower prevalence of memory dysfunction 6-48 months after ICU discharge


Health-Related Quality of Life for ARDS Survivors

- Metanalysis of data from 5 studies using the Short Form-36
- All 8 domains below the age & sex matched population normal
- Mental health & physical domains most impacted
- Larger decrements in 4 physical domains (physical functioning, role physical, bodily pain & general health perception)
- Long term physical & cognitive impairments exists up to 2 years after incident

Rubenfeld GD et al. Chest 2007; 131:554-562
Dowdy DW et al. Intensive Care Med, 2006;32:1115-1124
“Coming together is a beginning. Keeping together is progress. Working together is success.”

Henry Ford