ARDS/ALI: Partnering with Multidisciplinary Evidence-Based Care Practices to Impact Patient Outcomes

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Disclosures

- Sage Products Speaker Bureau & Consultant
- Hill-Rom Speaker Bureau & Consultant
- Eloquest Healthcare
Objectives

• Describe the causes of and the major pathophysiologic manifestation in ARDS/ALI
• Discuss the various multidisciplinary evidence-based care practices surrounding the prevention of VAP, ventilator management (PEEP) and fluid administration to maximize oxygen delivery (PIPES & PUMP)
• Outline various interventions to impact care of patients with ALI/ARDS through reducing O2 demand (Paralysis), positioning therapies (Position) and advanced nutritional support (Protein) and examine ARDS/ALI interventions

Presentation Overview

◆ Defining Acute Lung Injury/ARDS
  • Links with the Systematic Inflammatory Response Syndrome
  • Incidence & mortality
◆ Pathophysiologic derangements
◆ Clinical signs & symptoms
◆ Supportive care: The 7 P’s of therapy
  • Prevention, PEEP, Pipes, Pump, Paralysis & Positioning, Protein
◆ 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** - \( \frac{\text{PaO}_2}{\text{FiO}_2} < 300 \) 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

**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

PaO$_2$ = 70 torr  \( \text{FiO}_2 = 60\% \) or .60  
\[ \text{P/F Ratio} = \frac{70}{.60} \]  
Answer: 117

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**Acute Respiratory Distress Syndrome**

- **Timing**  -  Acute Onset
- **Oxygenation**  -  \( \frac{\text{PaO}_2}{\text{FiO}_2} < 200 \) 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

Potential New Definition

- A known predisposing factor (direct/indirect)
- Radiographic infiltrates with diffuse (bilateral) alveolar edema
- Severe hypoxemia ($\text{PaO}_2 / \text{FiO}_2$) at 12-36hrs after onset. ($< 200\text{mmHg on FiO}_2 \geq 0.5 \& \text{PEEP} \geq 10$)
- Left ventricular failure excluded (Echo)
- Specific biomarker or markers (currently non available)


190,000 ARDS Patient per Year
74,000 Deaths/41% Mortality
3.6 Million Hospital Days

Rubenfeld GD et al. Chest 2007; 131:554-562
Clinic ICU practice including low tidal volume ventilation for all patients, a restrictive transfusion policy, sepsis and pneumonia treatment protocols, and increased intensivist staffing contributed to the observed decline in hospital-acquired ARDS/ALI.
Characteristics of Patients With Greater Chance of Development or Higher Morality

**Development**
- Higher BMI’s associated with ↑ incidence
- Sepsis*
- Witnessed aspiration
- Severe trauma
- Massive transfusion (>15 unit in 24hrs)
- Drug overdose
- Pancreatitis
- Near-drowning
- Inhalation injury

**Mortality**
- Dependent on clinical risk factor
- Older patients
- Male gender
- African American
- Alcohol abuse
- Cigarette smoking
- Septic shock in patients with diabetes (lower mortality)
- Ventilation strategy


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
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

Basilar Atelectasis / Wet lung
Pulmonary Vascular Injury

<table>
<thead>
<tr>
<th>Cause</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Stress fractures of capillaries</td>
<td>Leaky membranes</td>
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<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

- Increase right ventricular work
- Right ventricle fails
- Decrease flow to left ventricle
- Decrease stroke volume
- Decrease cardiac output
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

Nursing Diagnoses Illustrated:
Impaired Gas Exchange
Clinical Manifestations

- Refractory hypoxemia
- Pulmonary shunting
- Pulmonary hypertension
- Other organ system failures
- Decreased lung compliance
- Diffuse alveolar and interstitial infiltrates

Clinical Manifestations

- Refractory Hypoxemia
- Pulmonary Shunting
Clinical Manifestations

- Refractory hypoxemia
- Pulmonary shunting
- Pulmonary hypertension
- Other organ system failures
- Decreased lung compliance
- Diffuse alveolar and interstitial infiltrates

Ware LB, Matthay MA. N Engl J Med, 2000;342:1334
Impact of Organ Failure With ARDS

Dorinsky & Gadek, Chest, 2007;132:829-835
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
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 demostrated 73% sensitive, 79% specific for progression to ALI

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

• Early transfusion of PRBCs & or FFP is an independent predictor for the development of ARDS in adult trauma patients. (> 5 units in 1st 24hrs post admission) Each PRBC unit ↑ risk by 6%. Chaiwat O, et al. Anesthesiology, 2009;110:351-60
• TPN administration is independently associated with late ARDS. Pluard d, et al. Injury, 2009;40:511-515

PREVENTING THE INVASION

- VAP/VAC
- CLA-BSI
- SSI
- CA-UTI
Ventilator Associated Pneumonia Risk Factor Categories

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

Comprehensive Evidence-Based Clinical Practice Guidelines: Prevention

- Recommend
  - Oral intubation route
  - New vent circuit for each patient
  - Circuit change if soiled or damaged
  - Change HME q 7 days
  - Use of closed suction, changed each patient and clinically indicated
  - Subglottic drainage if expected >72 ventilation
  - HOB 45 (when impossible as near)

- Consider
  - Rotational therapy
  - Oral antiseptic rinses

- Not recommended
  - Bacterial filters
  - Use of isegan

- No recommendations made
  - Use of systematic search for sinusitis, aerosolized antibiotics, intranasal mupirocin
  - Type of airway humidification
  - Timing of trach
  - Prone positioning

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


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)

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)


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

• 4 RCT’s Lower vs. Higher $V_T$ (1149 patients)
• 3 RCT’s Lower vs. Higher PEEP (2299 patients)
• 2 RCT’s Higher $V_T$ & Lower PEEP vs. Lower $V_T$ and Higher PEEP (148 patients)

Results:
• Lower $V_T$ at same PEEP vs. High $V_T$ reduced hospital mortality ($p=0.02$)
• Higher PEEP alone did not reduce mortality ($p=0.08$)
• Higher PEEP reduced the need for rescue therapies for life threatening hypoxemia ($p < 0.001$) and death ($p < 0.001$) in patients receiving rescue therapies


Evidence: What is the Purpose if We Do Not Use It?

• Large variation exist in implementation of the evidence
• Standardized protocols and monitoring help improve compliance
• Compliance decreases over time
• Nurse or respiratory driven protocols improve compliance

Jones, TL. Worldviews on Evidence Based Nursing. 2011;8(1):40-50
Recruitment Strategies

- Optimal PEEP
- Sustained Inflation: 30-40cm of CPAP for 30 seconds (Cardiac & respiratory adverse effects)
- Prone positioning

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, 2011;1)
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
• Trail 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)

*p<.001

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

- 3 trails, 2299 patients
- No difference in mortality with High vs. Low PEEP for entire population
- High PEEP vs. Low PEEP in ARDS patients showed significant reduction in mortality (p=0.049)
- Rates of pneumothorax and vasopressor use were similar

Current Cochrane Review Underway

Briel M. et al. JAMA, 2010;303(9):865-873

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

Esteban A. Am J Respir Crit Care 1999;159:512-18
Esteban A. Am J Respir Crit Care 1997;156:459465
“Non-Conventional” Ventilator Strategies

- APRV
- 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
High Frequency Oscillation Meta-analysis

- 8 Trials/Methodology good (n=419)
- FiO2 at 24, 48 and 72hrs was 16-24% higher in patients receiving HFO
- HFOV likely to improve mortality and not likely to cause harm
- Large trial currently underway (2yrs before outcomes known)


CESAR Study: Conventional Ventilation Vs. ECMO

- Multicenter, randomize trial, 766 screened/180 adults, 18-65 yrs, potential reversible ARDS
- Randomized to transfer to ECMO center or continue to receive conventional care at a tertiary center
- Excluded if vented for > 7 days, FiO2 > 80%, PIP > 30
- 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 (p=03)

NNT = 6

Multinational Early ECMO Study Underway

EOLIA

PIPES & 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

Outcomes the same irrespective of patients baseline serum albumin.

SAFE investigators, BMJ, 2006;333:1044-6


Fluid Management Fight

counter to achieve lowest possible PCWP consistent with adequate cardiac output by fluid restriction &/or diuretics

Ensure adequate blood volume to maximize O2 delivery to the tissues.
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 mortality with negative balance on day 4 (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
- Consider push-pull after hemodynamically stable

Early resuscitative fluid administration & later conservative fluid management impacts survival in Septic Shock patients with ALI
PARALYSIS

Balancing Oxygen Supply and Demand
"OKAY, LET'S GET THOSE EYEBALLS MOVING!!"

O$_2$ Supply Debt
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) and lower impact on PTSD.
- Wake up and breathe protocol resulted in ↓ time on ventilator, ↓ ICU & hospital stay and reduced 1 year mortality (NNT=7)
- When dexmedetomine was compared to midazolam in long term sedation, it showed ↓ time to extubation, ↓ ICU stay, ↓ delirium prevalence and ↑ delirium free days, problems with Bradycardia

Riker RR, et al. JAMA, 2009;301:1489-499
Sneak Peek at New Guidelines

• PAD Guidelines Coming (Evidence Based)
  • Pain (Non-pharm & Pharmacological-Remifentanil or Fentanyl)
    • BPS (Behavioral Pain Scale)
    • CPOT (The Critical Care Pain Observation Tool)
  • Agitation (non-benzodiazepine, Dexmedetomidine or Propofol) light sedation & interruption
    • RASS
    • SAS
  • Delirium (use atypical antipsychotics-Olanzapine/Quetiapine)
    • ICU-CAM
    • ICU Delirium Screening Checklist
• PAD Bundle

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
Neuromuscular Blockade in Early ARDS

- Multicenter, double blind trial
- 340 patients with ARDS within 48hrs of admitted to ICU
- ARDS defined as P/F ratio of < 150
  PEEP 5cm & Vt of 6-8 ml/kg PBW
- Randomized to receive 48hrs of cisatracurium or placebo
- Study did not use train of 4

Results:
- After risk adjustment NMB group showed improved mortality at 90 days (31.6% vs. 40.7%)
- Also significant at 28 days
- ↑time off vent
- No difference in muscle weakness

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Odds ratio (fixed) 95% CI</th>
<th>Odds ratio (fixed) 95% CI</th>
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<tbody>
<tr>
<td>Pneumonia and prophylaxis</td>
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<tr>
<td>Demarest et al™</td>
<td>4/14</td>
<td>3.45 (0.72, 1.72)</td>
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<td>Fink et al™</td>
<td>7/18</td>
<td>14.55 (0.89, 0.65)</td>
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<td>Gentilellio et al™</td>
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<td>7.58 (0.13, 1.42)</td>
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<tr>
<td>Kelley et al™</td>
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<td>6.77 (0.36, 1.30)</td>
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<td>Kirschenbaum et al™</td>
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<tr>
<td>Traver et al™</td>
<td>8/12</td>
<td>10.24 (0.21, 1.42)</td>
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<tr>
<td>Whiteman et al™</td>
<td>10/23</td>
<td>8.04 (0.08, 1.86)</td>
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<tr>
<td>deBoisblanc et al™</td>
<td>6/69</td>
<td>9.95 (0.12, 1.01)</td>
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<td>108/333</td>
<td>72.49 (0.27, 0.58)</td>
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Test for heterogeneity: $\chi^2 = 4.63$, df = 8 (P = .85), $\hat{\tau}^2 = 0$
Test for overall effect: $Z = 4.68$ (P < .001)

Pneumonia treatment

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<td>Ahrens et al™</td>
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<td>27.51 (0.18, 0.67)</td>
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Test for heterogeneity: not applicable
Test for overall effect: $Z = 3.12$ (P = .002)

Subtotal (95% CI) 14/17

Test for heterogeneity: $\chi^2 = 4.16$, df = 9 (P = .90), $\hat{\tau}^2 = 0$
Test for overall effect: $Z = 5.63$ (P < .001)

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<td>100.00 (0.38, 0.53)</td>
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</table>

Figure 4 Meta-analysis of pneumonia (with subgroups of prophylaxis and treatment for respiratory dysfunction): rotation versus control

Goldhill DR et al. Amer J Crit Care, 2007;16:50-62
CLRT to Prevent VAP

Methodology
- Prospective randomized controlled trial, 3 medical ICUs at a single center
- Eligible if ventilated < 48 hours & free from pneumonia, ALI or in ARDS
- 150 patients with 75 in each group
- 35 CLRT patients allocated to undergo percussion before suctioning
- Measures to prevent VAP were standardized for both groups including HOB

Results: CLRT vs. Control
- VAP: 11% vs. 23% p = .048
- Ventilation duration: 8 ± 5 days vs. 14 ± 23 days, p = .02
- LOS: 25 ± 22 vs. 39 ± 45 days, p = .01
- Mortality: no difference

Where Does The Prone Position Fit into A Mobility Program for ARDS Patients?

“Unless otherwise contraindicated a trial of proning should be attempted in those receiving ventilatory support whose impaired oxygenation fails to respond to usual measures, including sedation, recruiting maneuvers, and PEEP. Protein should be limited to those with severe ARDS (PaO2/FiO2 ratio < 100 mmHg) who show convincing positive recruitment within a few hours.”

Marini JJ. Intensive Care Medicine, 2010;36:559-560.
Prone Positioning Meta-analysis: 2011

Meta-analysis:

• 7 RCT’s: 1675 patients of which 862 ventilated prone ALI/ARDS and ARDS alone (4 studies/LPV & duration)
• Relationship between effect size & duration of prone position examined
• Examine major airway side effects

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<td>Timmers 2009</td>
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Major Airway Complications

Non-significant trend towards benefit based on duration in the prone position

Protein
(Nutrition)

Prevention of Malnutrition, Therapeutic Modulation of Vital Organ Function & Support of Immunity, Inflammation & Antioxidant Defenses
Meta-analysis on Enteral Nutrition: Does The Type of Feeding Make a Difference

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

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

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

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 voluntary 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)


OMEGA Study

• RCT, multicenter trail
• 272 adults within 48hrs of developing ALI requiring MV whom intended to start enteral feeds
• Intervention: Twice day enteral supplement of n-3 fatty acids, y-linolenic acid and antioxidants compared with isocaloric feeds
• Outcome: VFD
• Results:
  • Study stop early for futility
  • Showed potential harm

EDEN RCT: Initial Trophic vs. Full Enteral Feed in ALI Patients

- Multicenter RCT (44 hospitals-ARDS Network)
- 1000 patients 48hrs post ALI development requiring ventilation
- Randomized to Trophic or Full for first 6 days
- If still needed post 6 days, given full feeding
- Results
  - Baseline characteristics similar
  - Full group received more calories
  - No difference in VFD’s
  - No difference in 60 day mortality
  - No difference in infectious complications
  - Trophic feeding resulting in less gastrointestinal intolerance

Pharmacological Treatment

The Unsuccessful Eighth “P” of ARDS Management

EBR: Pharmacologic Therapies in ALI/ARDS

- 33 RCT’s, 3272 patients
- Excluded NO, partial liquid ventilation
- No effect on mortality
  - Prostaglandin E
  - N-Acetylcysteine
  - Early high dose corticosteroids
  - Surfactant
  - Statins? (may be to early to tell)
- Some benefit but smaller trials
  - Low dose corticosteroids late phase
  - Pentoxifylline (30 patients) (clinical data insufficient)

Adhikari, et al. Cochrane Database of Systemic Reviews, 2010
Multicenter Surfactant Trial


ARDS Subgroup Surfactant Benefit

Positive Impact on Mortality & VFD’s in Patients with ALI/ARDS Caused by Pneumonia or Aspiration

RCT in Progress with rSP-C

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

Methodology:
• 14 trials randomly/1303 patients met inclusion criteria
• 10 trials had a high risk of bias
• Methodology criteria good

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

Not Recommended for Routine Use in ALI

ALTA Trial (Albuterol for the Treatment of ALI)
• Phase III ARDS Network RCT Trial
• To be included need to meet the definition of ALI and/or ARDS
• Terminated after 1st interim analysis (282 patients)
• No difference seen in 60 day mortality or ventilator free days between placebo & beta-2 agonist (Albuterol)

Presented by Dr. Matthay at a Scientific Symposium at UCSF 2009
Meta-analysis: Steroids in ALI/ARDS

- 12 trails
- 966 patients
- No improvement in hospital mortality
- Significant reduction in hospital mortality in low dose group (2mg/kg or less (p=.03)
- Quality of the evidence low
- Strongest in ALI/ARDS with consensus definition


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

No evidence from RCT’s to support or refute the use of PLV in ARDS/ALI. Need more studies.

The Future

- Preventing Progression
- Bundling of Supportive Care
- New Ventilator Modes?
- New Pharmacological agents
Long Term Outcomes
Functional Disability 5 Years after ARDS

- 109 survivors of ARDS at 3, 6, 12 months, 2, 3, 4 & 5 yrs
- Interviewed, pulmonary function tests, 6 minute walk test, resting & exercise oximetry, chest imaging, quality of life & reported use of health services
- Results:
  - Median 6 minute walk distance 436m (76% of predicated)
  - Physical component score of medical outcomes was 41 (mean norm score matched for age & sex, 50)
  - Pulmonary function normal or near normal
  - Constellation of other physical & psychological problems develop or persisted in pts & family caregivers for up to 5 yrs


It Takes a Village

“Coming together is a beginning. Keeping together is progress. Working together is success.”

Henry Ford
Are You A Team of Experts or an Expert Team?

Together
Everyone
Achieves
More
When would NOW be a good time to do this?

It is not enough to do your best; you must know what to do, and THEN do your best.
~ W. Edwards Deming