ARDS: Moving Beyond Tidal Volume

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Overview

• Fluid management for ALI patients
  – The septic ALI patient
• PEEP strategies
  – Other ventilator management approaches
• Pharmacotherapy
• “Rescue” therapies
Fluid Management: Physiology

- Pulmonary edema formation (even noncardiogenic) increases with rise in hydrostatic pressure
- Increased EVLW associated with poor outcomes
- Concern for decreased organ perfusion with “dry lung” strategy

Adapted from Staub Chest 1978
FACTT: Factorial trial design

**Fluid Management**

<table>
<thead>
<tr>
<th></th>
<th>&quot;Conservative&quot; (n = 500)</th>
<th>&quot;Liberal&quot; (n = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC CATHETER</td>
<td>250 patients</td>
<td></td>
</tr>
<tr>
<td>CVC CATHETER</td>
<td>250 patients</td>
<td>250 patients</td>
</tr>
</tbody>
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NHLBI ARDS Network, *NEJM* 2006
Baseline hemodynamics in FACTT

- 8.1% had CI < 2.5 L/min/m²
- 2.5% had PAOP > 18 mmHg and CI < 2.5 L/min/m²

29% PAOP > 18 mmHg

~50% of these = 19 or 20 mmHg
Fluid Conservative vs. Fluid Liberal Strategies

- Fluid conservative targets:
  - CVP < 4 mm Hg
  - PAOP < 8 mm Hg

- Fluid liberal targets:
  - CVP < 10 mm Hg
  - PAOP < 14 mm Hg

- Management with protocol delayed until patient out of shock for at least 12 hours
Cumulative fluid balance in FACTT

-2000

0

2000

4000

6000

8000

ml of fluid

Liberal
Conservative

Study Day

0 1 2 3 4 5 6 7
“Liberal” fluid strategy approximates usual fluid management
FACTT Fluid Strategy and Outcomes

- Compared with fluid liberal group, fluid conservative strategy resulted in:
  - 2.5 more ventilator-free days (p<0.001)
  - No difference in 60-day mortality
    - 25.5% vs. 28.4%, p=0.30
  - 2.2 more ICU-free days (p<0.001)
  - Trend towards reduced need for dialysis
    - 10% vs 14%, p=0.06
Translating FACTT to the Real World

- Patients must be out of shock and off vasopressors for > 12 hours before fluid conservative management
- Net fluid balance at 7 days in conservative arm = ZERO
- Patients with established need for dialysis excluded
- Simplified protocol in use by ARDS Network
**Simplified Fluid Conservative Protocol**

<table>
<thead>
<tr>
<th>CVP, mm Hg</th>
<th>MAP ≥ 60 mm Hg and Off Vasopressors for &gt;12 h</th>
<th>Average urine output &lt; 0.5 ml/kg/h</th>
<th>Average urine output ≥ 0.5 ml/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8</td>
<td>Furosemide; reassess in 1h</td>
<td>Furosemide; reassess in 4h</td>
<td></td>
</tr>
<tr>
<td>4-8</td>
<td>Fluid bolus ASAP; reassess in 1h</td>
<td>Furosemide; reassess in 4h</td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>Fluid bolus ASAP; reassess in 1h</td>
<td>No intervention; reassess in 4h</td>
<td></td>
</tr>
</tbody>
</table>

*Furosemide: Begin with 20 mg bolus, 3 mg/h infusion, or last known effective dose. Double each subsequent dose until goal is achieved with max dose of 160 mg bolus or 24 mg/h. Do not exceed 620 mg/d. Diuretic therapy should be withheld for patients with renal failure (dialysis dependence, oliguria with serum creatinine > 2 mg/dl, or oliguria with urinary indices indicative of acute renal failure).*

** Fluid bolus: 15 ml/kg crystalloid, or 1 unit of packed RBCs, or 25g albumin.*

Calfee and Matthay, *Chest* 2007
Fluid Conservative vs. Early Goal-Directed Therapy

• Sepsis is most common cause of ALI
  – Fluid resuscitation with EGDT largely accepted as standard of care for early sepsis management

• Average time from ED admission to FACTT implementation: 43 hours

• Patients must be out of shock and off vasopressors for >12 hours before starting fluid protocol

• No conflict with early goal-directed therapy for sepsis
Questions about Utility of CVP

• Systematic review in *Chest* by Marik et al, 2008
  – CVP correlated poorly with fluid responsiveness and with measured blood volume
  – Methodologic issues: heterogeneity
  – Authors conclude that “CVP should not be used to make clinical decisions regarding fluid management.”

• Level of evidence: Randomized controlled trial data most compelling
Furosemide and Albumin in Hypoproteinemic Patients

- Serum total protein < 5-6 g/dL
- Furosemide infusion + albumin bolus q8h
- Improves oxygenation, fluid balance, and hemodynamics
  - No mortality benefit (small studies)
- SAFE trial (NEJM 2004) suggests that crystalloid should still be resuscitation fluid of choice

Martin GS et al, CCM 2002 and 2005
Summary: Fluid Management in Acute Lung Injury

• FACTT demonstrates that a fluid conservative approach reduces time spent on ventilator
  – Goal CVP < 4
  – Fluid balance net even over first week in ICU

• No conflict with early goal-directed therapy for sepsis

• Furosemide + albumin may be useful in hypoproteinemic patients
  – Larger studies still needed
PEEP Strategies: Rationale

• Increased PEEP leads to higher mean airway pressure
  – Promotes alveolar recruitment
  – Decreases “atelectrauma”

• Counter-argument: Increased PEEP may over-distend ventilated alveoli
  – Increased intra-thoracic pressures
Randomized controlled trials of higher PEEP in ALI/ARDS

- **ALVEOLI**: ARDS Network, *NEJM* 2004
  - Terminated for futility after enrollment of 549 patients
  - No mortality or time on ventilator benefit

- **Lung Open Ventilation (LOV)** from Canada, *JAMA* 2008
  - N=983
  - No mortality or time on ventilator benefit

- **Positive End-Expiratory Pressure Setting in Adults (EXPRESS)**, *JAMA* 2008
  - N=767
  - No mortality benefit
  - More ventilator-free days in increased recruitment group
    - 7 vs 3, p=0.04
Esophageal Pressure Guided Strategy

• Rationale: Variable pleural and abdominal pressures in ALI patients --> unpredictable transpulmonary pressures for given PEEP
  – TPP = airway pressure - pleural pressure
  – Pleural pressure approximated with esophageal balloon
• 61 patients, all ventilated with 6 ml/kg
  – Control group: PEEP per ARDSnet protocol
  – Intervention group: PEEP adjusted to maintain transpulmonary pressure 0-10
  – Stopped at interim analysis for evidence of benefit

Talmor et al, *NEJM* 2008
Esophageal Pressure Guided Strategy

• Results:
  – Primary outcome: P:F ratio at 72 hours 88 mm higher in intervention group
  – Average PEEP significantly higher in intervention group (15-17 mm Hg)
  – Mortality rate at 28 days numerically lower in intervention group
    • Relative risk 0.43; 95% CI 0.17-1.07, p=0.06

• Critique: High percentage of patients with ALI due to abdominal pathology (~40%)

• Phase III randomized controlled trial planned
25 Years of Failed Drug Trials for ARDS

- Corticosteroids
- Surfactant
- Prostaglandin E1
- Anti-endotoxins
- Anti-cytokines
- Procysteine
- **Nitric oxide**
- Ibuprofen
- Ketoconazole
- Lisofylline
- Soluble neutrophil elastase inhibitor
- sPLA$_2$ inhibitor

Reviewed in Cepkova J Int Care Med 2006
Late Steroid Rescue Study, ARDS Network

• Data in early ARDS clear: Steroids do not reduce mortality
  – What about late, “fibroproliferative” ARDS?
• RCT of methylprednisolone vs. placebo in late ARDS, 8-28 days after onset (N=180)
• Results: No mortality benefit
  – Evidence of harm in patients enrolled > 14 d after ARDS
  – No increase in infections, but significant increase in neuromyopathy in steroid group

NEJM 2006
Recent Trials: Activated Protein C

- Liu et al, *AJRCCM* 2008
- Phase II RCT of APC vs. placebo, n=78
  - Stopped early by Data Safety Monitoring Board
  - Patients with severe sepsis excluded
  - Mortality 13%
- Treatment with APC increased Protein C levels (p=0.002)
  - Reduced pulmonary dead space
- No effect on mortality or ventilator-free days
“Rescue” Therapies

• Not proven to reduce mortality or improve outcomes
• Some evidence of physiologic benefit or improvement in other surrogate outcomes
  – May be an option when back is against the wall
• “Rescue” therapies include:
  – Proning
  – Inhaled NO
  – Extracorporeal life support (ECMO)
Proning

- Reduces perfusion to dependent, atelectatic lung
  - Promotes V/Q matching and recruitment of previously dependent alveoli
- Improves oxygenation in 70% of patients
- Does not improve mortality
  - Now shown in several randomized controlled trials
- Requires provider and staff expertise
  - Complications of turning procedure
  - Complications of prolonged prone position
Inhaled Nitric Oxide

• Recent meta-analysis of RCT’s in ALI: Adhikari et al, *BMJ* 2007

• Inhaled NO:
  – Improved P:F ratio (ratio of means 1.13; 95% CI 1.04-1.23)
  – Had no significant effect on mortality (RR 1.10, 95% CI 0.94-1.30)
  – Increased rate of new renal dysfunction (RR 1.50, 95% CI 1.11-2.02)
    • Mechanism still unclear

• May be suitable as rescue therapy but keep duration of treatment short
  – Start at low dose (1-5 ppm)
  – Beware of tachyphylaxis
Extracorporeal Life Support

- Initial trials showed very high mortality
- More recent studies demonstrate lower mortality rates
- CESAR: Large randomized controlled trial in UK has been completed
  - To be published soon
- Local expertise critical
Summary of ALI/ARDS Therapies Other than Low Tidal Volume

- Fluid conservative management strategy decreases time spent on ventilator
  - Aim for CVP<4, net even fluids over first week
  - Wait until patient out of shock for >12 hrs
- No mortality benefit to higher PEEP strategy
- No specific pharmacotherapies found effective
- Rescue therapies for severe ARDS include inhaled NO, proning, ECLS
  - Dependent on local availability
PaO$_2$/FiO$_2$

**P** = 0.07

- **Conservative**
- **Liberal**

Study Day: 0, 1, 2, 3, 4, 7
On study plateau pressure

P=0.002