Problems with ARDS Trials: Time for more splitting and less lumping?

B. Taylor Thompson MD
Massachusetts General Hospital
Professor of Medicine,
Harvard Medical School
ARDS Disclosures

Lilly - Co-PI, PROWESS-SHOCK

Astra Zeneca - DSMB Chair, Cytofab for sepsis

Hemodec - Co I, ECCO2R for severe ARDS

US Biotest - ARDS
Problems ARDS Trials?

- Nitric oxide
- Surfactant
- Perfluorocarbon
- Corticosteroids
- Prostaglandin E1
- Lysophylline
- Ibuprofen

- Procysteine
- Ketoconazole
- Streptokinase
- Neutrophil elastase inhibitor
- sPLA$_2$ Inhibitor
- rhAPC
- Albuterol/salmeterol

- Lower Vt
- ? Furosemide (FACTT)
- Cisatricurium
Still trying: current/recently completed trials

1. Surfactant
   - Calfactant (Willson, n=480)
2. VIP (Said, Phase I)
3. Corticosteroids (Antonelli, n=400)
4. VEGF (Kaner, Phase II)
5. Tenecteplase (Ashley, Genentec, Phase II)
6. Rosuvastatin (SAIL, ARDSnet, Phase III, n=1000)
7. Others…….170 trials on ClinTrials.gov!
“Success in science is defined as moving from failure to failure with undiminished enthusiasm”

Winston Churchill
Problems with ARDS Trials

• ARDS is a Syndrome
  – What are we studying?

• Do we really know if these drugs truly “failed”?
  – Are we measuring the right outcomes?
THE CONCEPTUAL MODEL OF ARDS

1. ARDS is a type of acute diffuse lung injury associated with recognized risk factors, characterized by inflammation leading to increased pulmonary vascular permeability and loss of aerated lung tissue.

2. The hallmarks of the clinical syndrome are hypoxemia and bilateral radiographic opacities (standard chest x-ray or CT scan).

Ranieri ESICM and CCCF, 2011. Proposed Berlin Definition of ARDS
<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Acute onset within 1 week of a known clinical risk factor or new/worsening respiratory symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypoxemia</strong></td>
<td>PaO$_2$/FiO$_2$ 201-300 with PEEP/CPAP ≥ 5</td>
<td>PaO$_2$/FiO$_2$ ≤ 200 with PEEP ≥ 5</td>
<td>PaO$_2$/FiO$_2$ ≤ 100 with PEEP ≥ 10</td>
</tr>
<tr>
<td><strong>Origin of Edema</strong></td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload**</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiological Abnormalities</strong></td>
<td>Bilateral opacities*</td>
<td>Bilateral opacities*</td>
<td>Opacities involving 3 + quadrants*</td>
</tr>
<tr>
<td><strong>Additional Physiological Derangement</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>$V_{E_{corr}} &gt; 10$ L/min or $C_{RS} &lt; 40$ ml/cmH$_2$O</td>
</tr>
</tbody>
</table>

*Not fully explained by effusions, nodules, masses, or lobar/lung collapse; use training set of CXRs
**Need objective assessment if no risk factor present (See table)

$V_{E_{corr}} = V_E \times \text{PaCO}_2/40$
Potential enrichment strategies to identify responsive subsets

- Direct vs Indirect Lung Injury
- Duration of ARDS (Early vs Late)
- Acute oxgenation response to PEEP
- Vascular Involvement
- Biomarkers/genetics
Direct vs Indirect Lung Injury: Surfactant

- No benefit for surfactant replacement in adults
- Post-hoc analysis suggested benefit in the subset with direct lung injury (pneumonia and aspiration)
- RCT of rSP-C Surfactant in **direct lung injury** failed to improve gas exchange or mortality
  - partial inactivation of rSP-C surfactant from re-suspension process introduced with this study
- Pediatric RCT in direct lung injury ongoing

Anzueto NEJM 1996; Spragg NEJM 2004; Taut Chest 2008; Spragg AJRCCM 2011
Direct vs Indirect Lung Injury: not so easy

- Three senior intensivists who had extensive experience with mechanical ventilation and ARDS used information from the hospital records to classify the patients as having direct or indirect ARDS
  - 37% of cases uncertain or mixed classification

Thille et al. Anesthesiology 2007
Biomarker for Direct (epithelial) Injury

- Elevated RAGE responders to VT reduction
- Large observational study on RAGE in ARDS began this year

Calfee, *Thorax* 2008; Clermont-Ferrand Clin Trial.gov
Potential enrichment strategies to identify responsive subsets

- Direct vs Indirect Lung Injury
- Duration of ARDS (Early vs Late)
- Acute oxygenation response to PEEP
- Vascular Involvement
- Biomarkers
Diffuse Alveolar Damage

• Acute exudative phase (hrs to days)
  – intraalveolar and interstitial edema
  – necrosis of type I alveolar lining cells
  – hyaline membranes, hemorrhage

• Fibroproliferative phase (days to wks)
  – cellular inflammation
  – alveolar and peribronchial fibrosis
  – vascular remodeling
↑ Mortality with Steroids after 14d of ARDS

Interaction $p=.0170$
Adjusted $p=.0878$

Steinberg NEJM 2006; Thompson Crit Care 2007
Potential enrichment strategies to identify responsive subsets

- Direct vs Indirect Lung Injury
- Duration of ARDS (Early vs Late)
- Acute oxygenation response to PEEP
- Vascular Involvement
- Biomarkers
FiO₂ 1, PEEP 0
PaO₂ = 125 mm Hg

FiO₂ 1, PEEP 10
PaO₂ = 176 mm Hg

PaO₂ = 410 mm Hg
Disparities in:

Mortality

Effects of interventions

Risk/Benefit ratio

PaO$_2$ = 410 mm Hg

FiO$_2$ 1, PEEP 10

PaO$_2$ = 176 mm Hg
Potential enrichment strategies to identify responsive subsets

- Direct vs Indirect Lung Injury
- Duration of ARDS (Early vs Late)
- Acute oxygenation response to PEEP
- Vascular Involvement
- Biomarkers
Microvascular Obstruction and Remodeling in ARDS

Normal human lung capillaries

Lung capillaries p 14 d ARDS

Morphometric analysis -> Thrombosis, medial thickening, decreased vascular density of pre- and intra-acinar vessels

Zapol Chest, 1977; Snow ARRD 1982
Macrovascular Obstruction in ARDS: Detection with Balloon Occlusion Pulmonary Angiography (BOPA)

- BOPA + in 19 of 40 between 1-17 days after ARDS onset
- Filling defects a/w 1) ARDS severity 2) presence of DIC 3) PA HTN 4) fatal outcome

Green et al ARRDS 1982
Pulmonary Dead-Space Fraction and Risk of Death in ARDS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>ODDS RATIO (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead-space fraction (per increase of 0.05)†</td>
<td>1.45 (1.15–1.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>SAPS II (per 1-point increase)</td>
<td>1.06 (1.03–1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quasistatic respiratory compliance (per decrease of 1 ml/cm of water)</td>
<td>1.06 (1.01–1.10)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Vd/Vt and Prognosis in ARDS

Mayo Clinic n=118

ARDSnet n=1,616

Vd/Vt = 1 - [(0.86 x VCO2) / (VE x PaCO2)]

Gajic, Critical Care 2011
Biomarkers of a procoagulant ARDS phenotype

Ware et al, Crit Care Med, 2007
Summary: Opportunities for enrichment?

• Surfactant for direct lung injury with ↑ RAGE
• HFO/RMs/Prone for the new “severe ARDS”
• Vascular targeted therapies for patients with elevated dead space, RV dilation, elevated BNP/troponin (vascular phenotype)
• Anticoagulants (aerosol heparin, rhAPC) for patients with hyper-coagulable phenotype

Frank and Thompson, Curr Opinion in Crit Care 2010
One last comment…

Do we really know that the drugs tested for ARDS are ineffective? Are we measuring the right outcomes?

Let’s examine the results of a hypothetical trial and see if it changes your practice?
Post-traumatic Stress Disorder (PTSD) and corticosteroids?

• Less PTSD and improved emotional well-being in sepsis survivors treated with corticosteroids in the ICU

• Lower cortisol levels during ARDS a/w higher PTSD rates in long term survivors

Haller CCM 1999; Hauer Brain Research 2009
Hypothetical Trial (n=6,000)

- Hydrocortisone is inexpensive, easy to administer, extensive clinical experience
- RCT of Hydrocortisone vs Placebo: Mortality primary
  - No change in mortality with small CIs
  - No change in VFDs or ICU LOS
  - No side effects, including no secondary infections or muscle weakness. Mild hyperglycemia.
  - Marked improvement in QOL @ 6 and 12 months
  - ↓ in rates of PTSD (40% -> 10%)?
  - 75% back to work vs 40% in placebo

- Positive or Negative? Would you use hydrocortisone?
Summary

1. New and old definitions identify a heterogeneous group of pts
   – Need “enrichment” strategies to identify subsets most likely to benefit
   – Potential for hysiologic, proteomic, and genomic stratification

2. We do not know if these drugs truly “failed”
   – Need to take a more complete measure of the effect of an intervention, including long term functional outcomes
Thank you
Beta Adrenergic receptor (ADBR2) polymorphism and outcome

- AA genotype of the ADBR2 rs1042717 is associated with reduced beta receptor translation and function
- Single center (n=589) and multicenter (VASST, n=616)
- AA genotype a/w:
  - Higher resting heart rate, higher norepinephrine dose
  - Higher mortality (HR 2.23, 1.3-3.7) replicated in VASST (HR 2.82)
    - Less inhibition of IL-6 \textit{in vitro} with norepinephrine
- Genotypic effect \textit{eliminated with} steroids

Nakada et al \textit{AJRCCM} 2010
Corticosteroids may improve outcomes in the subset with AA ADRB2 genotype.
60d Mortality (95%CI)
P 28.6% (19.8-38.4)
MP 29.2% (20.2-39.3)
“It is now clear that survivors of critical illness and ALI experience a substantial and prolonged negative impact across many domains of their subsequent quality of life.”

“Study of the impact of interventions on long-term quality of life and other functional outcomes after hospital discharge is of high value and should be a fundamental part of Phase III trials”
Mortality remains the most important endpoint
  – No proven surrogate marker for mortality
  – Mortality preferred over survival analysis (time to death)

Ventilator free days to day 28
  – Not patient centered, may not change when mortality does. No longer recommended as the sole primary endpoint.

No consensus on composite endpoints
“The reporting and interpretation of results of ALI clinical studies could be improved by use of a standardized description of methods, endpoints, and results. A standardized format in ALI trials for collecting data, including long-term quality-of-life and functional status outcomes, would facilitate patient-level metaanalyses from multiple trials and enhance collaborative efforts.”
Biological Markers with Diagnostic or Prognostic Potential in ARDS

- **Inflammation** - IL-6, IL-8, sTNFRI, CRP
- **Disordered Coagulation** - Protein C, PAI-1
- **Endothelial injury** - Von Willebrand factor antigen
- **Myocardial Injury** – Troponin, BNP
- **Alveolar epithelium** - SP-D, sTNFRI, & RAGE
- **Adhesion molecule** - sICAM-1
- **Fibroblast proliferation** - PCPIII
- **Elastin breakdown product** - Desmosine (urine)
- **Nitric Oxide Levels** – exhaled NO

Ware et al. Chest 2010; Matthay et al. AJRCCM 2010
William Osler

"... uncontrolled septicemia leads to frothy pulmonary edema that resembles serum, not the sanguineous transudative fluid seen in dropsy or congestive heart failure."

Osler W. McCrae T. The principles and practice of medicine, designed for the use of practitioners and students of medicine. 10th ed., 1233 pp. New York, Appleton; 1925
ARDS is a syndrome, not a diagnosis

• Steroid responsive conditions may present as ARDS
  – Cryptogenic Organizing Pneumonia (COP)\(^1\)
  – Acute Eosinophilic Pneumonia\(^2\)
  – PCP complicating AIDS\(^3\)

• Open Lung Biopsy for unresolving ARDS often changes therapy\(^4\)

\(^1\) Epler NEJM ‘85
\(^2\) Allen NEJM ‘89, Buchheit ARRD ‘92
\(^3\) Gagnon NEJM ‘90, Montaner, Ann Int Med ’90
\(^4\) Patel Chest 2004, others
2.5 more VFDs (p<0.002)
3.2 less days on vent in survivors (p<0.001)

Conservative 25.5%
Liberal 28.4%  p=0.3
No Difference at One Year
Low Quality of Life with Con or Lib Fluid Rx
Health Utilities Index Mark 2 by Fluid Rx

p=0.004 for trend
Vent Free Days (± SD)
Placebo  6.8 ± 8.5
Steroid  11.2 ± 9.4
Mortality with Steroids after 14d of ARDS

Interaction  $p = .0170$
Adjusted  $p = .0878$

Steinberg NEJM 2006; Thompson Crit Care 2007

Exudative
Proliferative
Fibrosis/Repair

Steinberg NEJM 2006; Thompson Crit Care 2007
2.5 more VFDs (p<0.002)
3.2 less days on vent in survivors (p<0.001)

Conservative 25.5%
Liberal 28.4%  p=0.3
No Difference at One Year
An Early PEEP/FIO₂ Trial Identifies Different Degrees of Lung Injury in Patients with Acute Respiratory Distress Syndrome

Jesús Villar¹, Lina Pérez-Méndez¹,², José López³, Javier Belda⁴, Jesús Blanco⁵, Iñaki Saralegui⁶, Fernando Suárez-Sipmann⁷, Julia López⁸, Santiago Lubillo¹,⁹, and Robert M. Kacmarek¹⁰, on behalf of the HELP Network*
ALI and ARDS: AECC Definition, 1994

• Acute onset (7 days)
• $P_aO_2/F_IO_2$
  \[
  \leq 200 = \text{ARDS}
  \]
  \[
  \leq 300 \text{ for Acute lung Injury or ALI}
  \]
• Bilateral infiltrates c/w pulmonary edema
• No evidence of LA Hypertension
Low Quality of Life with Con or Lib Fluid Rx
Health Utilities Index Mark 2 by Fluid Rx

$p=0.004$ for trend
AECC Definition: Strengths and Limitations

• Good Predictive Validity for mortality
  – Luhr et al
    • ALI (not ARDS) 42% mortality
    • ARDS 41% mortality
  – Rubenfeld et al
    • ALI 38% mortality

• Identifies responders to low tidal volume

• Limited Specificity for DAD
  • Autopsy series show no evidence of DAD in 33%
  • majority without DAD had pneumonia, hemorrhage, pulmonary edema

Luhr AJRCCM 1999; Rubenfeld NEJM 2005; Esteban Ann Int Med 2004; Gattinoni JAMA 2008
Tidal Volume Reduction Beneficial In All Subsets

Eisner et al. *AJRCCM* 2001
AECC Definition: Strengths and Limitations

- Good Predictive Validity for mortality
  - Luhr et al
    - ALI (not ARDS) 42% mortality
    - ARDS 41% mortality
  - Rubenfeld et al
    - ALI 38% mortality

- Identifies responders to low tidal volume

- Limited Specificity for DAD
  - Autopsy series show no evidence of DAD in 33%
  - majority without DAD had pneumonia, hemorrhage, pulmonary edema

Luhr AJRCCM 1999; Rubenfeld NEJM 2005; Esteban Ann Int Med 2004; Gattinoni JAMA 2008
41 patients with ARDS by AECC criteria

- Placed on standardized ventilator settings (Vt 7-8, PEEP 10, FiO$_2$ 1.0)
- 58.5% (24 patients) had P/F > 200 at 30 minutes (mean 310 +/- 74)
- ICU mortality 12.5% vs 53% (persistent ARDS)
THE CONCEPTUAL MODEL OF ARDS

3. Physiological derangements include increased pulmonary right-to-left venous admixture, increased physiological dead-space, decreased respiratory system compliance.

4. Morphological hallmarks are lung edema, inflammation, hyaline membrane, and alveolar hemorrhage (i.e., diffuse alveolar damage)

Ranieri ESICM and CCCF, 2011. Proposed Berlin Definition of ARDS