THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Michael Matthay, MD
UC San Francisco
Professor of Medicine and Anesthesia

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Michael A. Matthay, MD is a Professor of Medicine and Anesthesia at the University of California at San Francisco and a Senior Associate at the Cardiovascular Research Institute. He is Associate Director of the Intensive Care Unit. He received his AB from Harvard University and his MD from the University of Pennsylvania School of Medicine. He received an American Thoracic Society award for Scientific Achievement in 2002 and the UCSF Award for Outstanding Clinical Research in 2006, as well as the Lifetime Achievement Award in Mentoring at UCSF in 2013. He is a member of the American Association of Physicians.

Research Interests: Dr. Matthay’s basic research has focused on mechanisms of salt, water, and protein transport across the alveolar epithelium that account for the resolution of pulmonary edema. He has also studied the pathogenesis and resolution of pulmonary edema and the acute respiratory distress syndrome (ARDS). His recent research has also focused on the biology and potential clinical use of allogeneic bone marrow derived mesenchymal stromal (stem) cells for ARDS.
Acute Respiratory Distress Syndrome 1967-2019
What Have We Learned?

Disclosures

- Grant support for lab-based and clinical research from NHLBI (R01, R35, R42, U54)

- Grant support for Clinical Trials (NHLBI-U01 and Dept of Defense)

- Grant support for Cell-Therapy Network (Alpha Stem Cell Clinic – California Institute of Regenerative Medicine)

- Grant support for observational study of Pulmonary Hypertension and ARDS (Bayer)

- No conflicts for this presentation
The clinical pattern, which we will refer to as the respiratory-distress syndrome, includes:

- severe dyspnea
- tachypnea
- cyanosis that is refractory to oxygen therapy
- loss of lung compliance
- diffuse alveolar infiltration seen on CXR

12 patients (7 trauma, 4 viral infection, 1 pancreatitis)

Our Understanding of ARDS has Evolved

- Prognosis, Definitions & Pathology
- Epidemiology
- Pathophysiology & Modified Lung Injury Score
- Pathogenesis
- Impact of clinical trials
- Treatment – timing & the routes for therapeutic interventions
Mortality Risk in ARDS Depends on the Clinical Risk Factor Factors


Berlin Definition of ARDS – JAMA 2012

- **Timing**: Respiratory failure within 1 week of a known insult or new/worsening respiratory symptoms
- **Imaging**: Bilateral opacities on chest radiograph or CT not fully explained by effusion, collapse or nodules
- **Origin**: Respiratory failure not fully explained by cardiac function or volume overload (objective criteria such as echocardiography to exclude hydrostatic edema if no risk factor is present)
- **Oxygenation**: acute onset of hypoxemia defined as \( \text{PaO}_2/\text{FiO}_2 < 300 \) mmHg on at least PEEP 5 cmH\(_2\)O*
  - \( \text{PaO}_2/\text{FiO}_2 \) of 201-300 mmHg is mild ARDS
  - \( \text{PaO}_2/\text{FiO}_2 \) of 101-200 mmHg is moderate ARDS
  - \( \text{PaO}_2/\text{FiO}_2 \leq 100 \) mmHg is severe ARDS
The Acute Respiratory Distress Syndrome (ARDS)

• Classic pathology - diffuse alveolar damage (DAD) for patients with ARDS (Bachofen & Weibel, ARRD, 1997)

• However, ARDS pathology reveals diffuse alveolar damage in 45% of post-mortem lung samples in patients who met the Berlin Criteria for ARDS 1991-2010 (Thille, AJRCCM, 2013)

• Also the incidence of diffuse alveolar damage declined in the decade after institution of lung protective ventilation

Int Care Med, 2016
Epidemiology of ARDS in 2019 (Incidence & Prevalence)

- Incidence 200,000 annually in the US (NEJM, 2005) from 21 hospitals in Kings County in Washington
- SF Bay Area study at UCSF and Oakland Childrens’ hospitals identified 328 children with ARDS over 4 years (AJRCCM, 2005)
- International study – SAFE – Winter of 2014 - in 50 countries in cross-sectional analysis of 29,144 patients - 10% of ICU patients had ARDS by Berlin Definition with 23% incidence in ventilated patients (JAMA 2016).

Epidemiology of ARDS in 2019 (Mortality & Clinical Recognition, SAFE study)

- Mortality in the SAFE study – 35% mild ARDS; 40% for moderate ARDS; 46% for severe ARDS (JAMA 2016)
- Mortality attributable to ARDS itself versus associated comorbidities and chronic diseases not clear although mortality higher in immunocompromised subgroup
- Clinical recognition of ARDS was low at 51% in mild ARDS and 79% in severe ARDS in the SAFE study (JAMA 2016)
- Less than 2/3 of patients treated with lung protective ventilation with tidal volume < 8 ml/kg tidal volume predicted body weight
- ARDS common but under-recognized and under-treated
**Epidemiology of ARDS in 2019**

*(Trauma, TRALI, Environmental Factors)*

- Trauma related ARDS – incidence markedly reduced, perhaps secondary to reduction in use of crystalloid for resuscitation (*J Trauma Acute Care Surg*, 2013)
- Cigarette use, alcohol abuse and air pollution associated with higher incidence of ARDS (*AJRCCM*, 2015; 2016)
- TRALI lower incidence since exclusion of female donors for fresh frozen plasma (*Blood*, 2014)
- In-hospital ARDS reduced in incidence over 8 years, probably related to reduced use of blood products, less nosocomial pneumonia, and reduced use of higher tidal volumes in the OR and the ICU (*AJRCCM*, 2011)

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**Epidemiology of ARDS in 2019**

*(Genetic Factors)*

- Higher mortality for Hispanic and African American patients with ARDS though (*Crit Care Med*, 2009) and higher mortality in men than women with ARDS though mechanisms for these differences not well worked out yet
- Some genetic factors associated with risk for developing ARDS by GWAS not achieved at genome wide level for significance
- But candidate gene and pathway analyses revealed some potential contributors, such as ANGPT2 genetic variants in European ancestry that code for angiopoietin-2, mediator and marker of vascular injury (*Int Care Med*, 2018)
**Pathophysiology of ARDS – What Have We Learned?**

- Hypoxemia is the classic physiologic abnormality in ARDS, explained by alveolar edema and alveolar collapse, with low ventilation to perfusion lung units and intra-pulmonary shunting.

- However, in almost all ARDS trials the minute ventilation is twice normal (12 versus 6 liters per minute). Why?

- Either there is marked increase in carbon dioxide production or there is an increase in alveolar dead space (high ventilation to perfusion lung units).

- So we did a prospective study of 179 patients at SFGH and UCSF Parnassus over 3 years of early ARDS (first 24 hours)

**Dead Space and Mortality in Early ARDS**

![Box plot showing dead space fraction for survivors and non-survivors](image)
Pulmonary Dead Space Independently Predicts Mortality in Early ARDS

\[ \frac{V_{d}}{V_{t}} = \frac{(PaCO_2 - P_{5}CO_2)\text{ }}{PaCO_2} \]


**Ventilatory Ratio (VR) Estimates Dead Space in ARDS and Independently Predicts Mortality**


\[ VR = \frac{\dot{V}_E \text{ measured} \times P_{CO_2} \text{ measured}}{\dot{V}_E \text{ predicted} \times P_{CO_2} \text{ ideal}} \]

- \( \dot{V}_E \text{ predicted} \) is the predicted minute ventilation calculated as predicted body weight X 100 (mL/min), and \( P_{CO_2} \text{ ideal} \) is the expected arterial pressure of carbon dioxide in normal lungs if ventilated with the predicted minute ventilation. \( P_{CO_2} \text{ ideal} \) is set as 37.5 mmHg (5 kPa) for all patients.

- VR was an independent predictor of mortality in ARDS after adjusting for P/F, PEEP, and driving pressure in 520 ARDS patients at ZSFG (Kallet’s cohort)
The Potential Value of Quantifying Pulmonary Edema

• In our 4 point acute lung injury score, the scoring for bilateral infiltrates is of limited value

• A more detailed scoring system for the extent of pulmonary edema could be used to guide and assess therapy in ARDS

• Potential to provide outcome measures and guide clinical understanding of severity of illness

The RALE Score

• Radiographic Assessment of Lung Edema

<table>
<thead>
<tr>
<th>Assigned number</th>
<th>% of quadrant with consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
</tr>
<tr>
<td>1</td>
<td>0-25%</td>
</tr>
<tr>
<td>2</td>
<td>25-50%</td>
</tr>
<tr>
<td>3</td>
<td>50-75%</td>
</tr>
<tr>
<td>4</td>
<td>75-100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assigned number</th>
<th>Infiltrate Density of Each Quadrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hazy opacity</td>
</tr>
<tr>
<td>2</td>
<td>Moderate opacity</td>
</tr>
<tr>
<td>3</td>
<td>Dense opacity</td>
</tr>
</tbody>
</table>

• Total
  • Multiply the consolidation and density score of each quadrant (max = 12)
  • Sum all four quadrants (max = 48)
Calculating a RALE Score

<table>
<thead>
<tr>
<th>Score</th>
<th>RUL</th>
<th>RLL</th>
<th>LUL</th>
<th>LLL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIS</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CONS</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

RALE Study Design

- 174 patients from FACTT
  - 5 centers: Baystate, Greensboro, San Francisco, Vanderbilt, Wake
  - 174 available baseline chest radiographs
  - 159 available follow-up Day 3 chest radiograph
  - Available clinical outcomes
    - Baseline and cumulative fluid balance
    - Baseline and delta P:F ratio
    - VFD
    - 28 and 60 day mortality

- Independently assigned each CXR a RALE score
Average baseline RALE Score is associated with VFD at 28 days

![Graph showing the association between baseline RALE scores and VFD at 28 days with p = 0.009](image)

Average baseline RALE Score is independently associated with VFD at 28 days

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Beta Coefficient</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean RALE</td>
<td>-0.172</td>
<td>(-0.30, -0.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>-0.114</td>
<td>(-0.16, 0.02)</td>
<td>0.14</td>
</tr>
<tr>
<td>Gender</td>
<td>0.104</td>
<td>(-0.92, 4.80)</td>
<td>0.18</td>
</tr>
<tr>
<td>APACHE</td>
<td>-0.392</td>
<td>(-0.19, 0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.056</td>
<td>(-0.73, 0.47)</td>
<td>0.47</td>
</tr>
<tr>
<td>Etiology of ARDS (direct vs indirect)</td>
<td>-0.012</td>
<td>(-3.37, 2.92)</td>
<td>0.89</td>
</tr>
<tr>
<td>Baseline fluid balance</td>
<td>-0.045</td>
<td>(-0.45, 0.26)</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Higher average baseline RALE Scores are associated with 28 and 60 day mortality

*\( p = 0.007 \)

*\( p = 0.003 \)

Warren et al, Thorax, 2018

Mean RALE Score decreases over time in conservative arm

*\( p < 0.001 \)
New Lung Injury Score for ARDS
(probably still a 4-point score)

- Incorporate RALE score for extent of pulmonary edema
- Incorporate the Ventilatory Ratio to include measure of impaired CO₂ excretion
- Retain PaO₂/FiO₂ categories
- Retain the level of PEEP categories
  (Compliance too difficult to include because unreliable data on plateau airway pressure)

Pathogenesis of Acute Lung Injury – 2019
(Insights from Experimental & Clinical Studies)

- Alveolar epithelial injury critical for severity of ARDS
- Role of neutrophil extracellular traps (NETs)
- Role of plasma cell-free hemoglobin
- How current effective therapies evolved from experimental studies
- Multiple factors combine to produce ARDS
Impaired Alveolar Edema Fluid Clearance is Associated with Higher Mortality in Acute Lung Injury

Hospital Mortality (\%)

P < .02

Impaired/Submaximal
N = 69

Maximal
N = 10

Alveolar Fluid Clearance

Ware and Matthay, AJRCCM, 2001

Ware and Matthay, Am J Resp Crit Care Med 2001

Alveolar Fluid Clearance Decreases Inversely with Number of Vasopressors in Patients with Sepsis

Percent with Intact Alveolar Fluid Clearance (≥ 3%/h)

N=30 N=48 N= 23 N=15

0 1 2 3 or 4

Number of Vasopressors

Zeyed JF et al, AJP:Lung, 2012
Elevated Baseline RAGE (Alveolar Epithelial Marker) Identified Patients with Higher Mortality

Calfee CS et al, Thorax, 2008

Patients with High Baseline Plasma RAGE levels had the Most Benefit from Low Tidal Volume – Illustrates Predictive Enrichment Concept

Calfee CS, Ware LB, Eisner MD, Parson PE, Thompson BT, Matthay MA, Thorax, 2008
Staph Aureus-Induced Acute Lung Injury in Mice – Role of Neutrophil Extracellular Traps (NETs) and Treatment with DNase1 +/- antibiotics

Translation to patients with ARDS: Elevated Plasma NETs in Patients Who Died with ARDS

Higher Plasma NETs/DNase ratio in ARDS patients who died
Cell-Free Hemoglobin

- potent vasoconstrictor
- binds nitric oxide
- Ferryl (4+) hemoglobin is a critical mediator of injury
- Mouse models and ex vivo perfused human lung show injurious effects in sepsis
- Acetaminophen blocks the injurious effects of cell-free hemoglobin in sepsis on acute kidney injury
- Example of point of care biomarker available now

In 391 patients with severe sepsis, plasma levels of free hemoglobin are associated with hospital mortality

Janz DR et al, Crit Care Med 2013
Cell-free hemoglobin (CFH) in the perfusate increases vascular permeability in isolated perfused human lungs

A

B

N = 5 per group, * p = 0.047

N = 5 per group, * p = 0.027

Shaver et al, JCI Insight, 2018

What Have We Learned about Pathogenesis that Led to New Therapies for ARDS?

• All based on improvements in supportive care
  – Low Tidal Volume (ARMA)
  – Fluid Conservative Therapy (FACTT)
  – Also neuromuscular blockade and prone positioning
• All stimulated by pre-clinical studies that suggested potential clinical benefit
  – Deleterious effects of high tidal volume *
  – Elevated intravascular hydrostatic pressure increased pulmonary edema in acute lung injury demonstrated in animal models**
  – Note the timeline from bench to bedside (20-25 years)
Webb & Tierney, 1974; Parker, 1984, Dreyfuss, 1991*
Staub, 1978; Prewitt, 1981; Sznajder, 1986; Schuster, 1987**
Biologic studies in plasma after randomization provided insights into the mechanisms of how low tidal volume reduced lung injury in the ARMA Trial.

Reduced Plasma Levels in Lower Tidal Volume Group

- Lower levels of IL-6
- Lower levels of IL-8
- Lower levels of TNR1
- Lower levels of SP-D

Thorax, 2003
Crit Care Med, 2005
AJP:Lung, 2005

Lung Protective Ventilation Reduced Lung Endothelial and Epithelial Injury

Matthay, Ware, & Zimmerman. JCI, 2012
What Have We Learned about Heterogeneity from Secondary Analyses of ARDS Clinical Trials?

• Using latent class analysis for defining sub-groups of ARDS, Calfee and co-investigators have found a hyper and a hypo-inflammatory endotype in 5 clinical trials (ARMA, ALVEOLI, FACTT, SAILS, HARP-2)

• Emphasizes the potential value of using both biologic and clinical variables in defining ARDS for future interventions
**Hyperinflammatory Endotype 2 Has Higher Mortality in FACTT Trial**

<table>
<thead>
<tr>
<th></th>
<th>Endotype 1</th>
<th>Endotype 2</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>60-day mortality</td>
<td>21%</td>
<td>44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>22%</td>
<td>45%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventilator-free days (mean)</td>
<td>15</td>
<td>8.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Famous K et al, AJRCCM, 2017

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**A 3-Variable Model Accurately Identifies ARDS Endotype**

<table>
<thead>
<tr>
<th></th>
<th>FACTT Derivation Cohort</th>
<th>ARMA Validation Cohort</th>
<th>ALVEOLI Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top predictors from FACTT</td>
<td>AUC</td>
<td>AUC</td>
<td>AUC</td>
</tr>
<tr>
<td>3-variable model (IL-8, bicarbonate, TNF-1)</td>
<td>0.95</td>
<td>0.94</td>
<td>0.91</td>
</tr>
<tr>
<td>4-variable model (IL-8, bicarbonate, TNF-1, vasopressor use)</td>
<td>0.97</td>
<td>0.89</td>
<td>0.86</td>
</tr>
<tr>
<td>5-variable model (IL-8, bicarbonate, TNF-1, vasopressor use, total minute ventilation)</td>
<td>0.97</td>
<td>0.90</td>
<td>0.88</td>
</tr>
</tbody>
</table>
- Randomized controlled trial of simvastatin for ARDS conducted in UK/Ireland
- N=540
- Simvastatin 80 mg vs placebo
- Patients enrolled within 48 hrs of meeting ARDS criteria
- No difference in ventilator-free days, mortality

McAuley D et al, NEJM 2014

Calfee CS et al, Lancet Resp Med, 2018
Survival Analysis to 28 Days – Simvastatin Reduced Mortality in the Class 2 Patients

Timing and Routes for Intervention for ARDS or Early Acute Lung Injury – 2019

- Early acute lung injury can be identified in the Emergency Department & the Intensive Care Unit
- Point of Care biological markers can help focus therapies on the higher risk patients
- Need to integrate biologic and clinical factors in clinical trial design, using both predictive and prognostic strategies
- Combination therapies may be needed, including beta agonists and steroids or cell-based therapies such as mesenchymal stromal cells
Pneumonia and Sepsis in the Emergency Department
Early Acute Lung Injury

Panel A – Lobar Bacterial Pneumonia
Panel B – Worsening Hypoxemia leading to Intubation
Panel C – Bilateral Infiltrates with ARDS plus CVP line for vasopressors


Clinical Trials of Early Acute Lung Injury - Pneumonia and Sepsis in the Emergency Department

• Gong M et al, LIPS-A - JAMA, 2016 – ASA for prevention (LIPS-A clinical criteria) – limited value because less than 10% of patients identified who progressed to develop ARDS

• Festic ... Levitt, Crit Care Med, 2018 – Inhaled steroids/beta agonists early treatment – successful phase 2a trial that reduced hypoxemia.

• NHLBI funded Prevention and Early Treatment of Acute Lung Injury (PETAL Network)(VIOLET – Vitamin D) and now CLOVERS – Fluid Liberal vs Fluid Conservative/Vasopressors

• Frat JP et al, NEJM, 2015 – tested three modes of oxygen delivery in severe hypoxic respiratory failure in spontaneously breathing patients in the ED - high flow nasal oxygen decreased mortality and decreased the intubation rate in patients with P/F < 200 mmHg.
What are the Next Steps to Optimize Treatments for ARDS?

- Need bedside point of care biologic assays in the ED and ICU to advance a personalized medicine strategy in critically ill patients with sepsis or early ARDS, such as plasma Hb and perhaps IL-8, Protein C, and bicarbonate

- Need to test prospectively these biologic measures in conjunction with the physiologic (RALE score, Dead Space, PaO₂/FiO₂, and PEEP), and clinical factors for classifying and stratifying patients (vasopressor shock for example)

- Test new treatments in the Emergency Department for early Acute Lung Injury (pneumonia and sepsis)

- Earlier recognition of ARDS and uniform implementation of low tidal volume are important