THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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

Friday, January 18, 2019 – 8:05 a.m. – 8:55 a.m.

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?**

Michael A. Matthay, MD

Departments of Medicine & Anesthesia

Cardiovascular Research Institute
University of California, San Francisco

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 Lancet · Saturday 12 August 1967

ACUTE RESPIRATORY DISTRESS IN ADULTS

DAVID G. ASHBAUGH
M.D. Ohio State
ASSISTANT PROFESSOR OF SURGERY

D. BOYD BIGELOW
M.D. Colorado
ASSISTANT IN MEDICINE AND AMERICAN THORACIC SOCIETY-NATIONAL
TUBERCULOSIS ASSOCIATION FELLOW IN PULMONARY DISEASE

THOMAS L. PETTY
M.D. Colorado
ASSISTANT PROFESSOR OF MEDICINE

BERNARD E. LEVINE
M.D. Michigan
AMERICAN THORACIC SOCIETY-NATIONAL TUBERCULOSIS ASSOCIATION
FELLOW IN PULMONARY DISEASE*

*From the Departments of Surgery and Medicine,
University of Colorado Medical Center, Denver, Colorado, U.S.A.*

"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
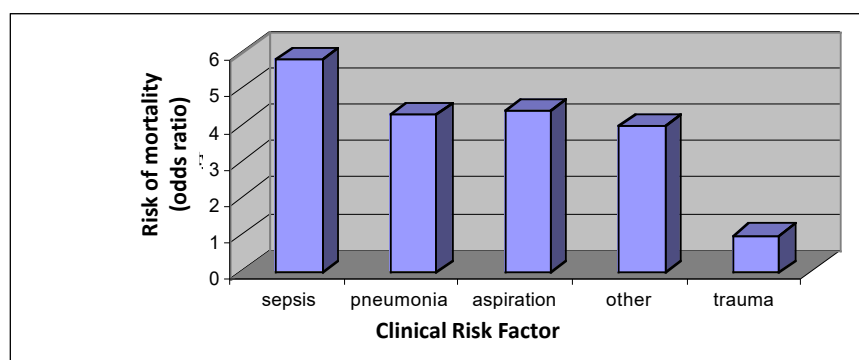

Eisner et al, Am J Resp Crit Care Med 164:231, 2001

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 PaO_2/FiO_2 <300 mmHg on at least PEEP 5 cmH_2O***
    - PaO_2/FiO_2 of 201-300 mmHg is mild ARDS
    - PaO_2/FiO_2 of 101-200 mmHg is moderate ARDS
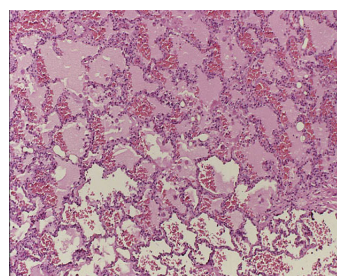   - PaO_2/FiO_2 ≤100 mmHg is severe ARDS

The Acute Respiratory Distress Syndrome (ARDS)
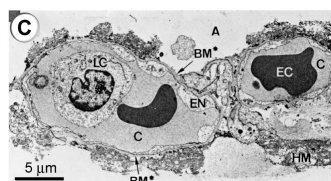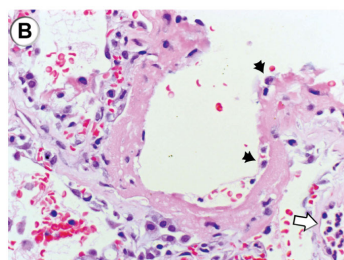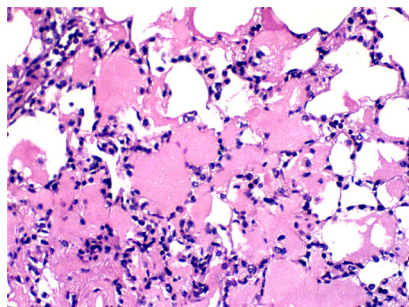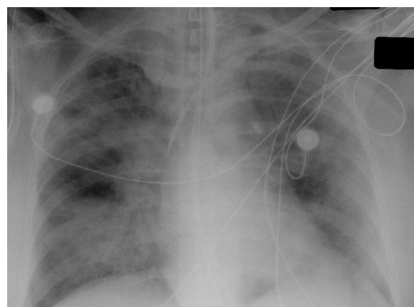
ARDS Pathology - 2019
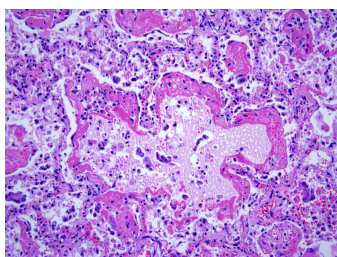
- Classic pathology - diffuse alveolar damage (DAD) for patients with ARDS (Bachofen & Weibel, *ARRD*, 1997)

- 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)

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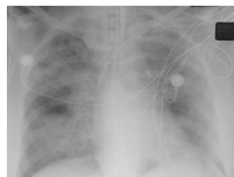
- Hypoxemia is the classic physiologic abnormality in ARDS, explained by alveolar edema and alveolar collapse, with low ventilation to perfusion lung units and intra-pulmonary shunting.

- 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
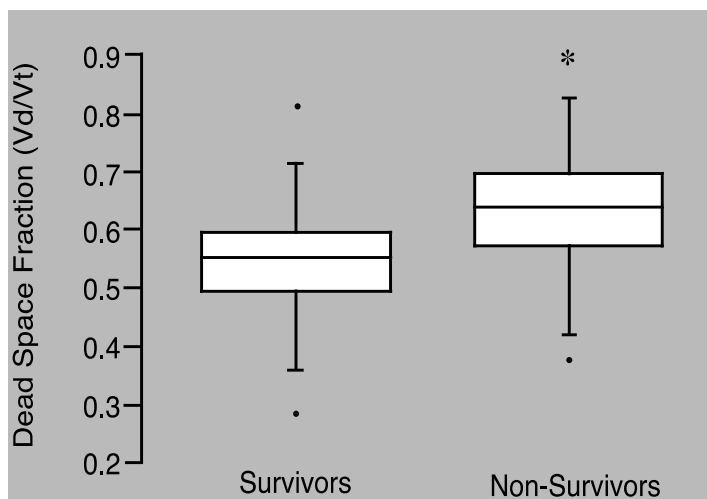
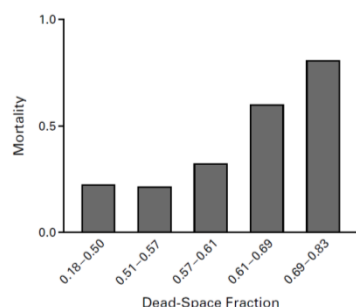## Pulmonary Dead Space Independently Predicts Mortality in Early ARDS

TABLE 3. ODDS RATIOS FOR VARIABLES INDEPENDENTLY ASSOCIATED WITH AN INCREASED RISK OF DEATH.*

VARIABLE	ODDS RATIO (95% CI)	P VALUE
Dead-space fraction (per increase of 0.05)†	1.45 (1.15−1.83)	0.002
SAPS II (per 1-point increase)	1.06 (1.03−1.08)	<0.001
Quasistatic respiratory compliance (per decrease of 1 ml/cm of water)	1.06 (1.01−1.10)	0.01

$$Vd/Vt = (PaCO_2 - P_ECO_2)/PaCO_2$$

Nuckton, T. J. *et al.* Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N. Engl. J. Med.* **346,** 1281–1286 (2002).

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

- **Physiological Analysis and Clinical Performance of Ventilatory Ratio in ARDS *Am J Resp Crit Care* Med, 2018, Pratik Sinha, Carolyn S Calfee, Jeremy Beitler, Neil Soni, Michael A Matthay, Kelly Ho and Richard H Kallet**

- $$VR = \frac{\dot{V}_{E\ measured}\ X\ Pa_{CO_2\ measured}}{\dot{V}_{E\ predicted}\ X\ Pa_{CO_2\ ideal}}$$

- $\dot{V}_{E\ predicted}$ is the predicted minute ventilation calculated as predicted body weight X 100 (mL/min), and $Pa_{CO_2\ ideal}$ is the expected arterial pressure of carbon dioxide in normal lungs if ventilated with the predicted minute ventilation. $Pa_{CO_2\ ideal}$ 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

- **R**adiographic **A**ssessment of **L**ung **E**dema

Assigned number	% of quadrant with consolidation
0	Clear
1	0-25%
2	25-50%
3	50-75%
4	75-100%

Assigned number	Infiltrate Density of Each Quadrant
1	Hazy opacity
2	Moderate opacity
3	Dense opacity

- Total
  - Multiply the consolidation and density score of each quadrant (max = 12)

- Sum all four quadrants (max = 48)

Calculating a RALE Score
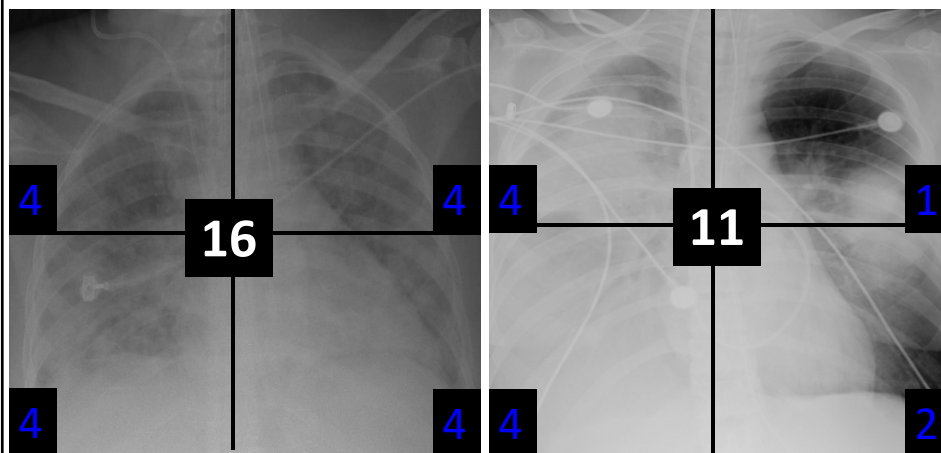
Figure 1A. Comparison of 2 CXR Scores

Score	RUL	RLL	LUL	LLL	Total
LIS	1	1	1	1	4
CONS	4	4	4	4	16

Figure 1B. Comparison of 2 CXR Scores

Score	RUL	RLL	LUL	LLL	Total
LIS	1	1	1	1	4
CONS	4	4	1	2	11

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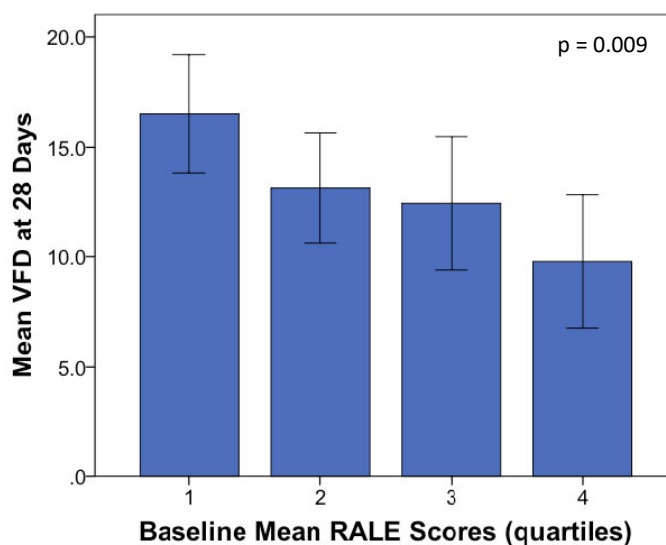
## Average baseline RALE Score is independently associated with VFD at 28 days

Predictors	Beta Coefficient	Confidence Interval	P value
Baseline mean RALE	-0.172	(-0.30, -0.01)	0.03
Age	-0.114	(-0.16, 0.02)	0.14
Gender	0.104	(-0.92, 4.80)	0.18
APACHE	-0.392	(-0.19, 0.78)	<0.001
BMI	-0.056	(-0.73, 0.47)	0.47
Etiology of ARDS (direct vs indirect)	-0.012	(-3.37, 2.92)	0.89
Baseline fluid balance	-0.045	(-0.45, 0.26)	0.58

Higher average baseline RALE Scores are associated with 28 and 60 day mortality

*p = 0.007

*p = 0.003
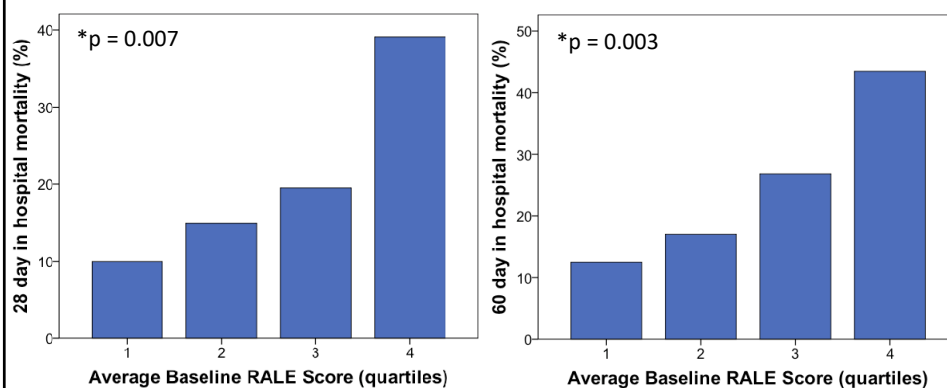
Warren et al, Thorax, 2018

Mean RALE Score decreases over time in conservative arm

Baseline avg RALE
Day 3 avg RALE

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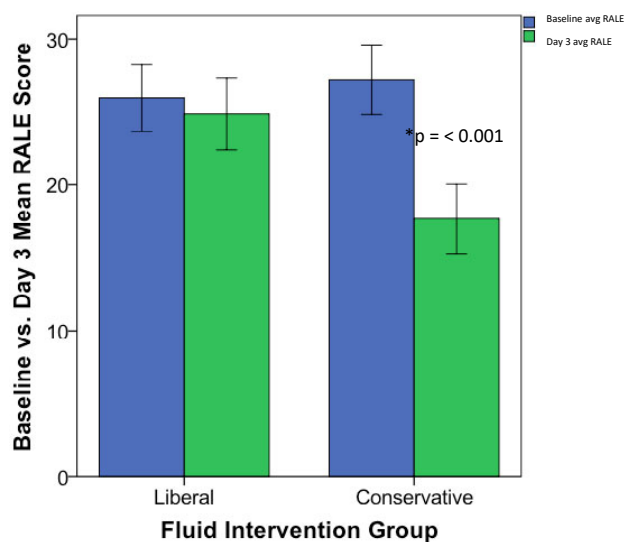
New Lung Injury Score for ARDS
(probably still a 4-point score)

- Incorporate RALE score for extent of pulmonary edema
- Incorporate the Ventilatory Ratio to include measure of impaired CO_2 excretion
- Retain PaO_2/FiO_2 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**

Ware & Matthay,

13
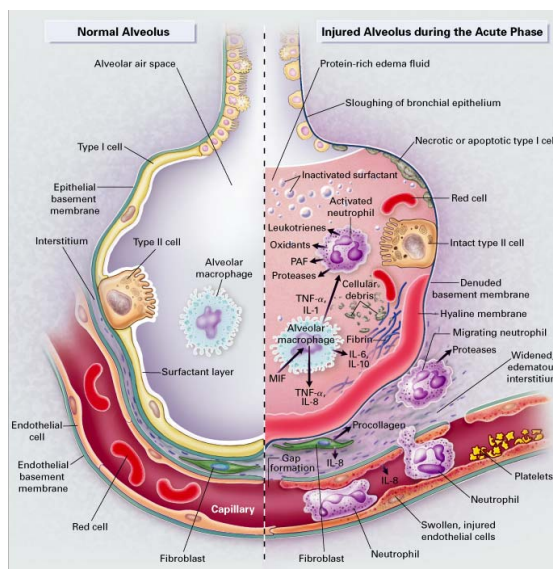
Impaired Alveolar Edema Fluid Clearance is Associated with Higher Mortality in Acute Lung Injury
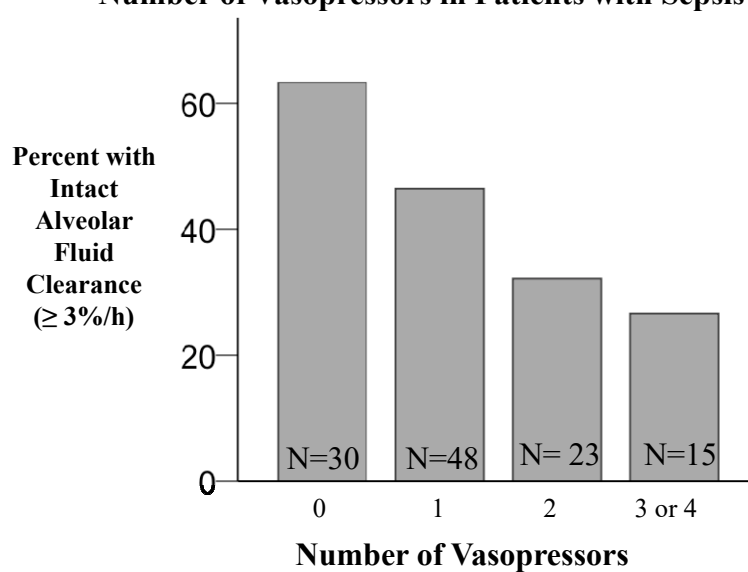
Hospital Mortality (%)

Impaired/Submaximal
N = 69

Maximal
N = 10

P < .02

**Alveolar Fluid Clearance**
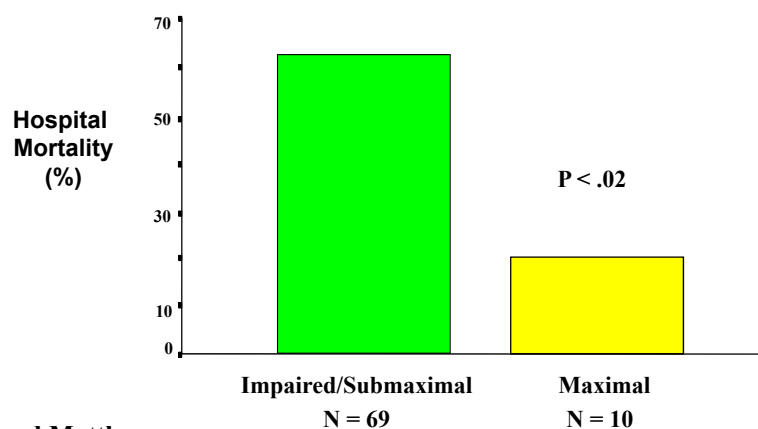
Ware and Matthay, AJRCCM, 2001

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 ($\geq 3\%/h$)

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
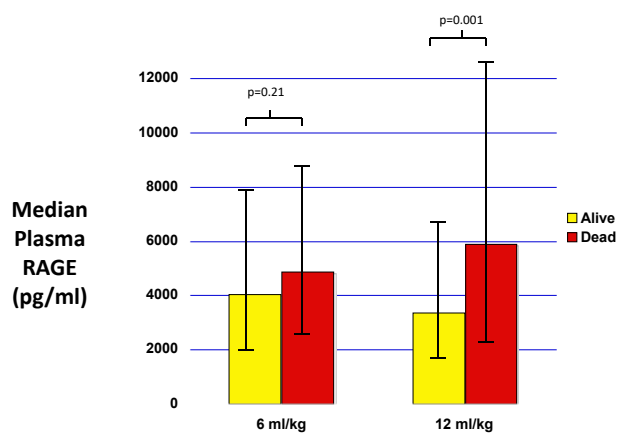
Calfee CS et al, *Thorax, 2008*

Patients with High Baseline Plasma RAGE levels had the Most Benefit from Low Tidal Volume – Illustrates Predictive Enrichment Concept
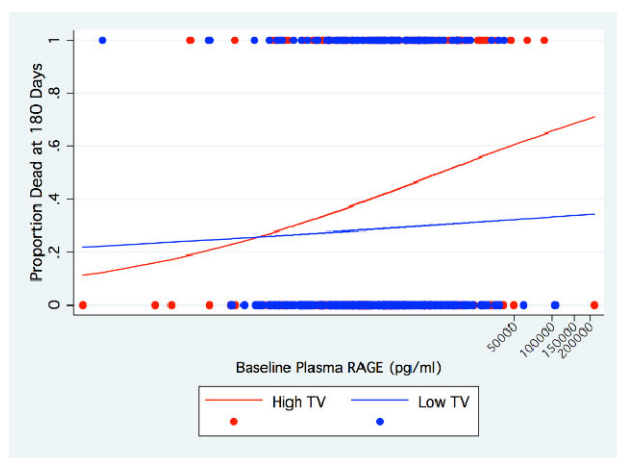
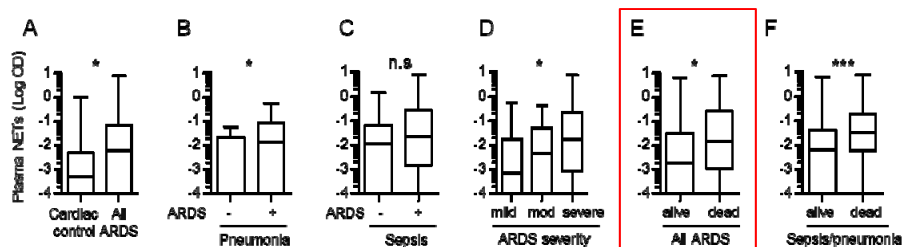Calfee CS, Ware LB, Eisner MD, Parson PE, Thompson BT, Matthay MA, Thorax, 2008

Staph Aureus-Induced Acute Lung Injury in Mice – Role of Neutrophil Extracellular Traps (NETs) and Treatment with DNase1 +/- antibiotics
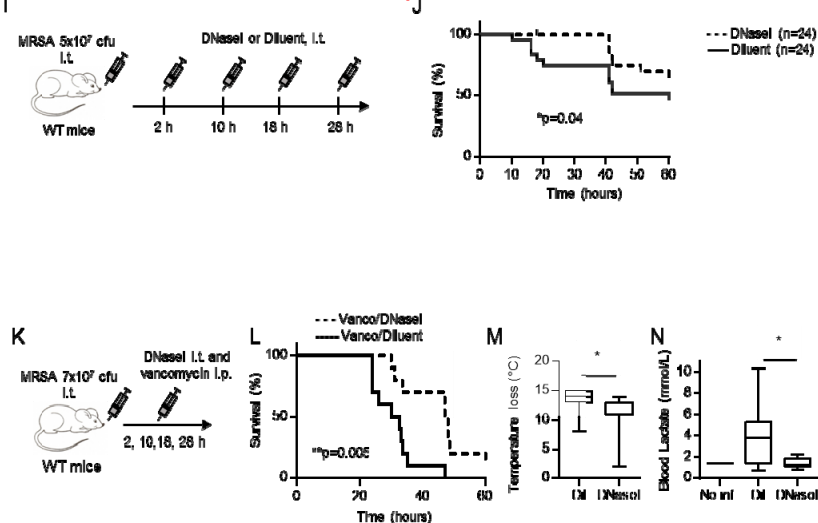
Lefrancais E, *et al. JCI Insight*, 2018

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

Higher Plasma NETs/DNase ratio in ARDS patients who died

Lefrancais E, *et al. JCI Insight*, 2018.

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
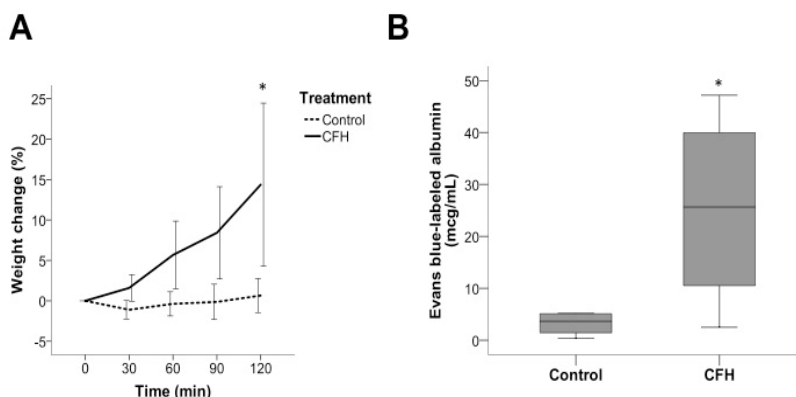- Example of point of care biomarker available now
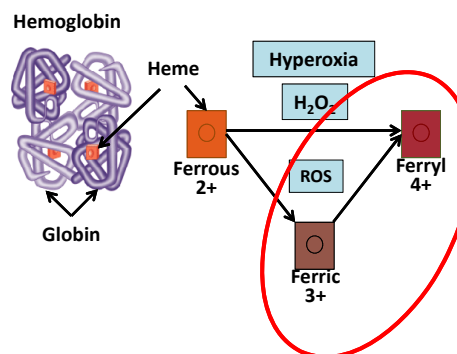
In 391 patients with severe sepsis, plasma levels of free hemoglobin are associated with hospital mortality
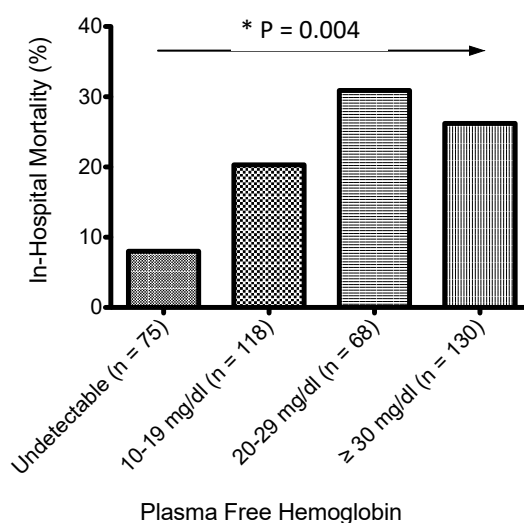
Janz DR et al, Crit Care Med 2013

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**

36

Biologic studies in plasma after randomization provided insights into the mechanisms of how low tidal volume reduced lung injury in the ARMA Trial

P=0.005

Mortality (Per Cent)

6 ml/kg   12 ml/kg

ARDS Network, NEJM, 2000
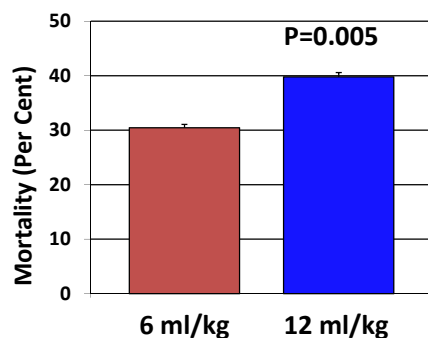
Reduced Plasma Levels in Lower Tidal Volume Group

- **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**

37

Lung Protective Ventilation Reduced Lung Endothelial and Epithelial Injury
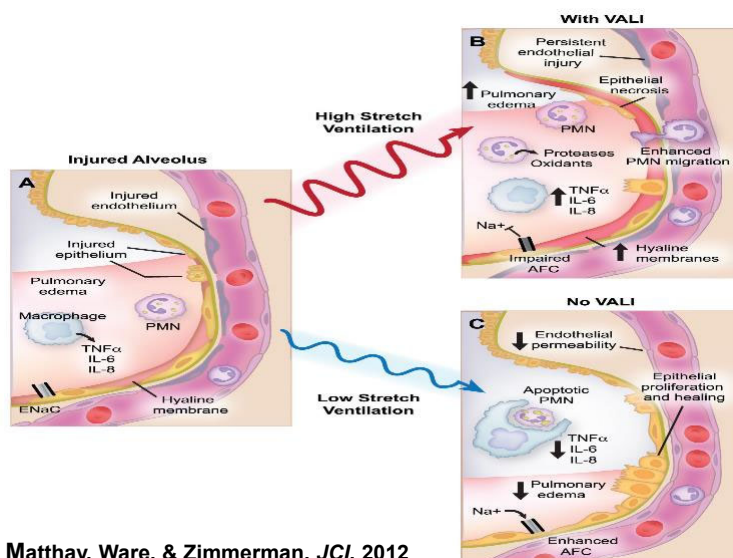
Matthay, Ware, & Zimmerman. *JCI*, 2012

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
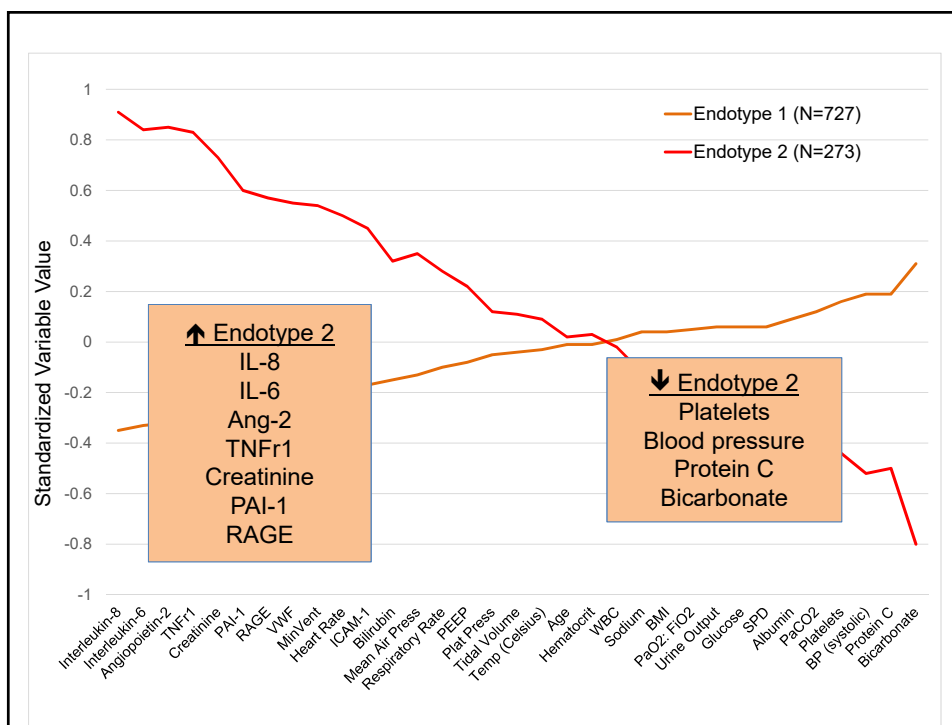
Hyperinflammatory Endotype 2 Has Higher Mortality in FACTT Trial

	Endotype 1	Endotype 2	p-value
60-day mortality	21%	44%	<0.0001
90-day mortality	22%	45%	<0.0001
Ventilator-free days (mean)	15	8.8	<0.0001

Famous K et al, AJRCCM, 2017

A 3-Variable Model Accurately Identifies ARDS Endotype

	FACTT Derivation Cohort	ARMA Validation Cohort	ALVEOLI Validation Cohort
Top predictors from FACTT	AUC	AUC	AUC
3-variable model *(IL-8, bicarbonate, TNFr1)*	0.95	0.94	0.91
4-variable model *(IL-8, bicarbonate, TNFr1, vasopressor use)*	0.97	0.89	0.86
5-variable model *(IL-8, bicarbonate, TNFr1, vasopressor use, total minute ventilation)*	0.97	0.90	0.88

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O'Kane, Ph.D.,
Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D.,
Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D.,
Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators,
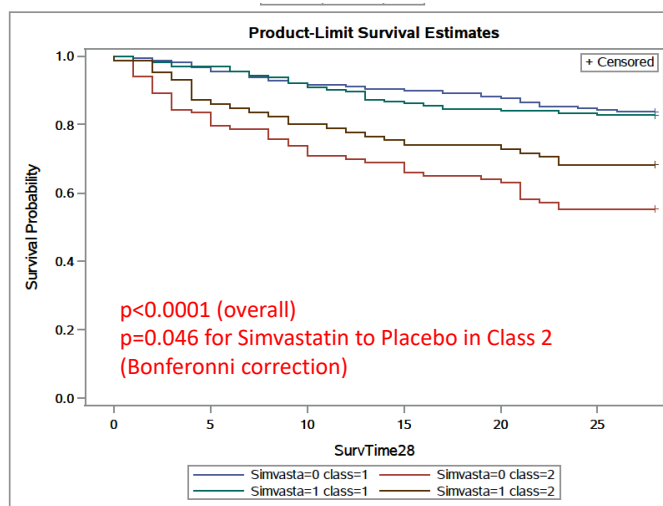for the Irish Critical Care Trials Group*

- 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
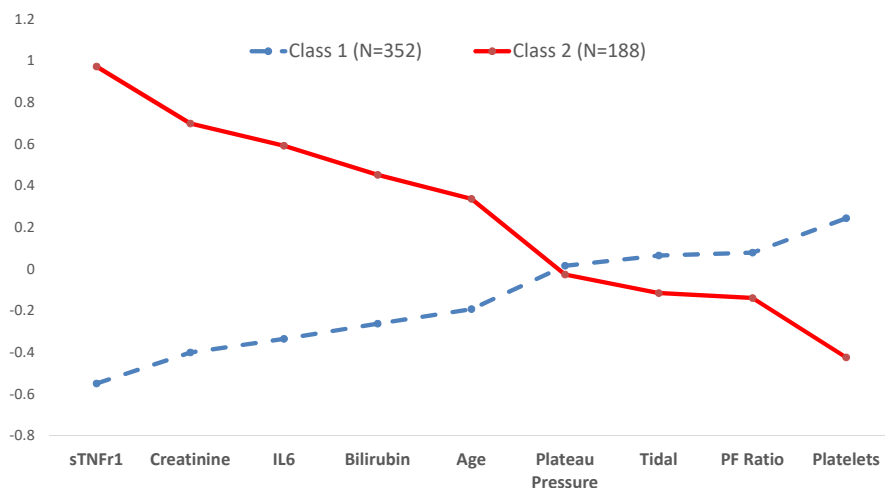
Calfee CS et al, Lancet Resp Med, 2018

Survival Analysis to 28 Days – Simvistatin Reduced Mortality in the Class 2 Patients

Product-Limit Survival Estimates

+ Censored

p<0.0001 (overall)
p=0.046 for Simvastatin to Placebo in Class 2
(Bonferonni correction)

SurvTime28

Simvasta=0 class=1 — Simvasta=0 class=2
Simvasta=1 class=1 — Simvasta=1 class=2

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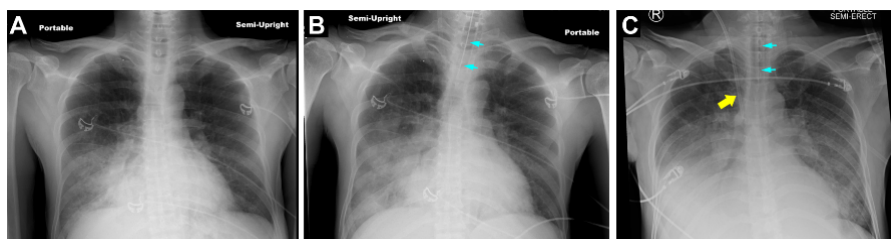
Panel A – Lobar Bacterial Pneumonia
Panel B – Worsening Hypoxemia leading to Intubation
Panel C – Bilateral Infiltrates with ARDS plus CVP line for vasopressors

Matthay, et al. Lancet Resp Med, 2017

47

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 hypoxemic 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. 48

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, PaO_2/FiO_2 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