What Should We Know about ARDS after Berlin Definition

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Berlin Definition & Epidemiology of ARDS

Limitations of AECC Definition
(American-European Consensus Conference)

- Timing: No definition of Acute
- Oxygenation: Not consider the effect of PEEP on PaO_2/FiO_2
- ALI: Misinterpretation for ALI
- CXR: poor inter-observer reliability
- PAWP: High PAWP & ARDS may coexist; poor inter-observer reliability
- Risk factor: Not included in definition

(JAMA 2012; 307:2526-33)

Berlin Definition of ARDS

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild (No ALI)	200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

(JAMA 2012; 307:2526-33)

Better Prediction by Berlin Definition

Stage	Mortality	MV duration in survivors
Mild	27% (24-30)	5 days (2-11)
Moderate	32% (29-34)	7 days (4-14)
Severe	45% (42-48)	9 days (5-17)

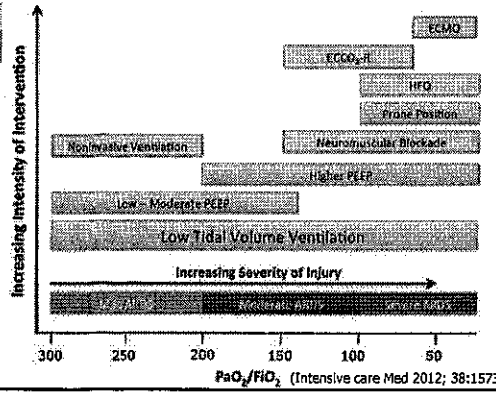
ROC curve: Berlin definition 0.577
AECC definition 0.536 (p<0.001)
(JAMA 2012; 307:2526-33)

Common Risk Factors for ARDS (not divide direct or indirect)

- Pneumonia
- Non-pulmonary sepsis
- Aspiration of gastric contents
- Major trauma
- Pulmonary contusion
- Pancreatitis
- Inhalational injury
- Severe burns
- Non-cardiogenic shock
- Drug overdose
- Multiple transfusion or TRALI
- Pulmonary vasculitis
- Drowning

(Intensive care Med 2012; 38:1573-82)

Therapeutic Options vs. Severity



(Intensive care Med 2012; 38:1573-82)

Trend of Incidence of ARDS

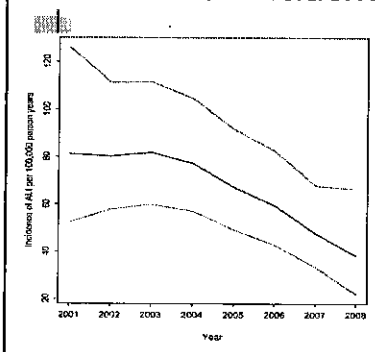


Figure 2. Trends in age- and sex-specific incidence of acute respiratory distress syndrome from 2001–2008 in Olmsted County, Minnesota; *dotted lines* represent 95% confidence intervals. ALI = acute lung injury.

- 58/100000 per year in USA (2005)
- Declining (2001-2008)
- perhaps due to:
  - Lung protective ventilation
  - Reduction of nosocomial Inf
  - Conservative use of blood products

(NEJM 2005; 353: 1685-93; AJRCCM 2011; 183:59-66)

Trend of Mortality of ARDS

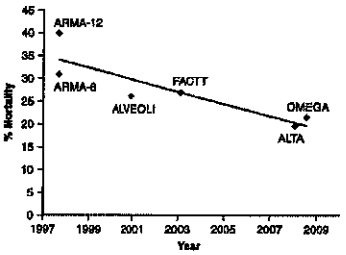
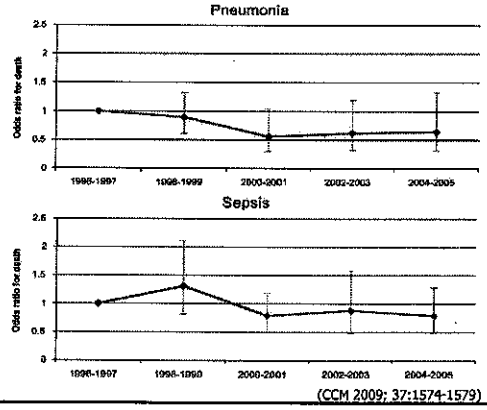


Figure 1 Observed 60 day mortality from ARDS Network clinical Trials from 1997 to 2009. ARMA, Acute Respiratory Distress Syndrome Management with Lower versus higher Tidal Volume (ARMA-6 patients received Vt of 6 ml/kg) (ARMA-12 patients received Vt of 12 ml/kg)[17]; ALVEOLI, Assessment of Low tidal Volume and Elevated End-expiratory Volume to Obviate Lung Injury[18]; FACTT, Fluid and Catheter Treatment Trial[19]; ALTA, Albuterol for the Treatment of ALI[20]; OMEGA, Omega-3 Fatty acid, Gamma-Linoleic Acid, and Antioxidant Supplementation in the Management of ALI or ARDS.[21] Adapted with permission from Spragg *et al.*[22]

- Mortality: 36-44% up to 2006
- Declining (1997-2009)
- Perhaps due to
  - Lung protective ventilation
  - Supportive Tx: Early antibiotics, Ulcer prevention, Better fluid Tx, Nutritional & organ support

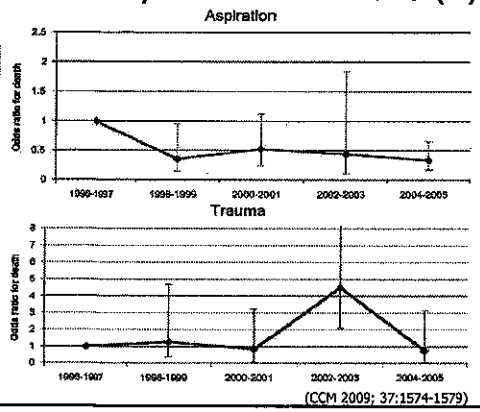
(J Clin Invest 2012; 122:2731-40; Postgrad Med J 2011; 87:612-22)

Mortality in ALI 1996-2005 (1)



(CCM 2009; 37:1574-1579)

Mortality in ALI 1996-2005 (2)



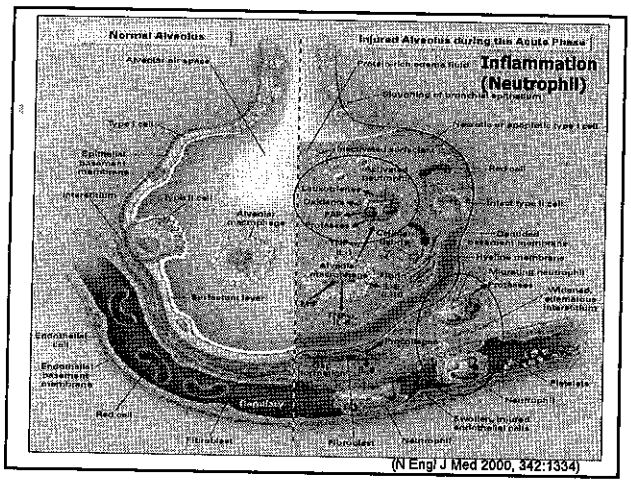
(CCM 2009; 37:1574-1579)

Pathophysiology of ARDS

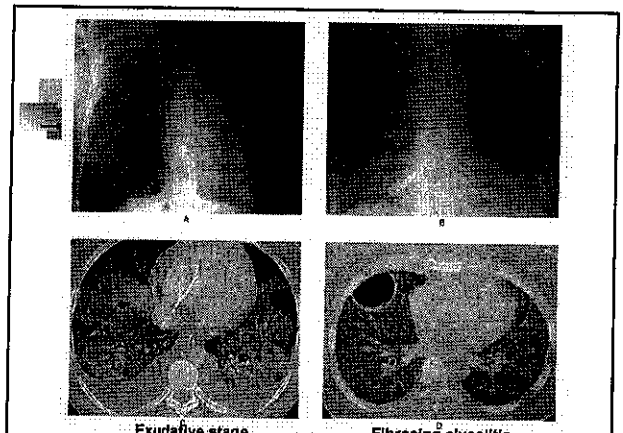
Pathogenesis of ARDS

- Dysregulated inflammation
  - Inappropriate accumulation & activation of leukocytes
    - Protease, Reactive oxygen species (ROS), Cytokines
  - Uncontrolled activation of coagulation pathways
- Alveolar barrier disruption
  - Increased permeability => alveolar flooding
  - Vascular endothelial cadherin (VE-cadherin)

(J Clin Invest 2012; 122:2731-40)

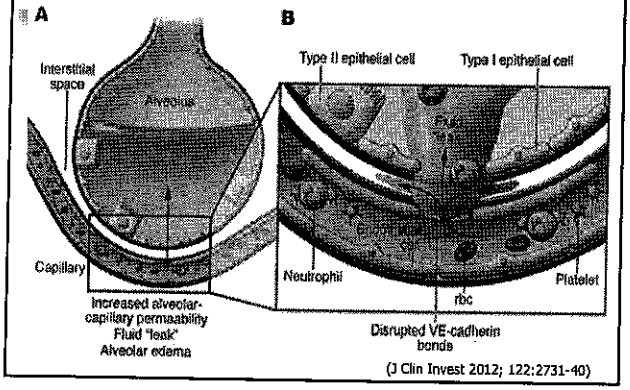


(N Engl J Med 2000, 342:1334)



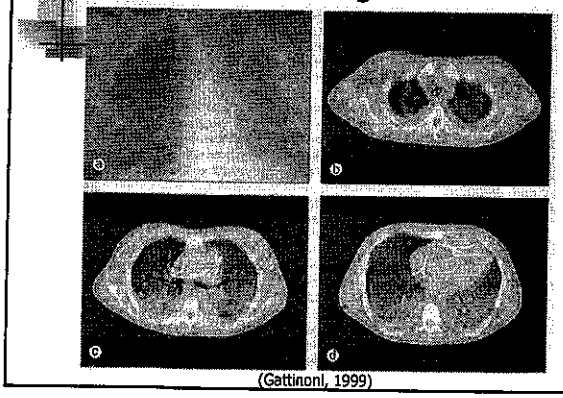
(N Engl J Med 2000, 342:1334)

Molecular Mechanisms of ARDS



(J Clin Invest 2012; 122:2731-40)

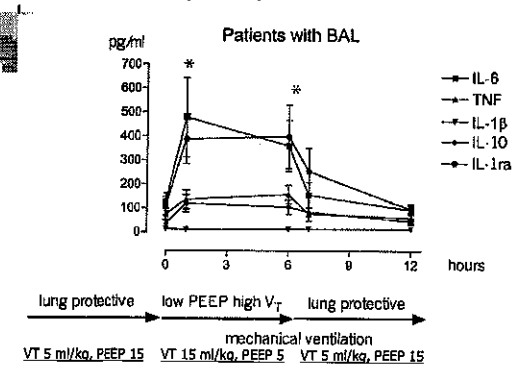
ARDS – Not homogenous


(Gattinoni, 1999)

Types of VILI

- Barotrauma:
  - Alveolar injury or rupture
- Volutrauma:
  - Parenchyma injury (ALI) due to overdistension (may be regional)
- Atelectrauma: open and close repetitively
- Biotrauma: activation of inflammation
  - Cellular response to volutrauma or atelectrauma
- Oxygen toxicity: oxygen derived free radicals

Reversibility of Cytokines in Plasma



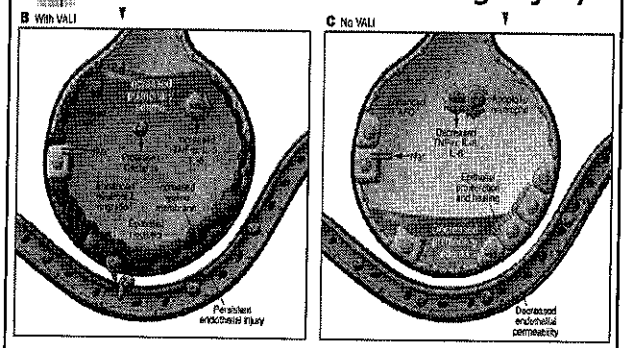
lung protective → low PEEP high V_T → lung protective

mechanical ventilation

VT 5 ml/kg, PEEP 15 | VT 15 ml/kg, PEEP 5 | VT 5 ml/kg, PEEP 15

(Intensive Care Med 2002;28:834-41)

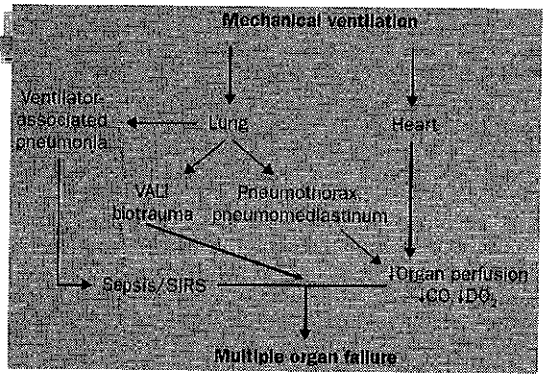
Ventilator Associated Lung Injury



AFC: alveolar fluid clearance

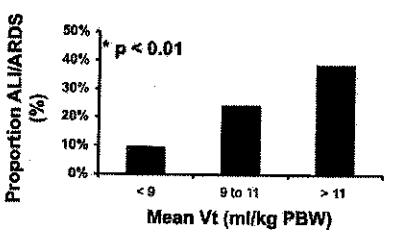
(J Clin Invest 2012; 122:2731-40)

MV as a Cause of MSOF



(Lancet 2003;361:332)

High VT is Associated with ALI after Severe Brain Injury



International Prospective study

GCS less 9

86 patients

Odd ratio: 5.45

95% CI: 1.54-19.24

Figure 1. Proportion of acute lung injury/acute respiratory distress syndrome (*ALI/ARDS*) according to tidal volume (*Vt*). Vt <9 mL/kg predicted body weight (*PBW*) (n = 21); Vt 9–11 mL/kg PBW (n = 47); Vt >11 mL/kg PBW (n = 14). *Adjusted *p* value from a stepwise regression model (Table 3).

(CCM 2007; 35:1815-20)

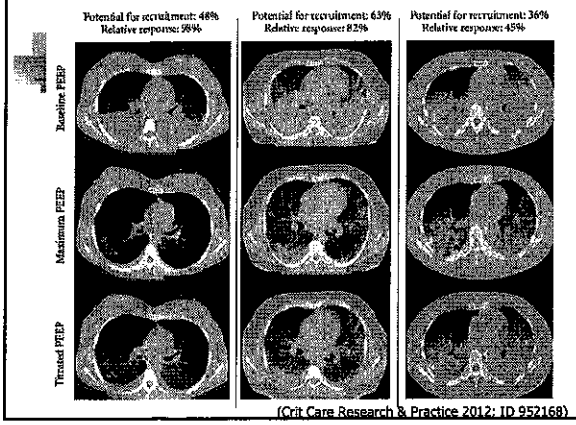
Diagnosis of ARDS

Diagnostic Tools (1)

- Imaging:
  - CXR: exclude other causes of hypoxemia
  - CT: exclude other less common conditions & interstitial diseases; assessment of recruitment (but need transport)
  - Ultrasonography: exclude pleural effusion & pneumothorax; potential study for recruitment

(Postgrad Med J 2011; 87:612-22)

CT Evaluation of Adequate PEEP & Recruitment

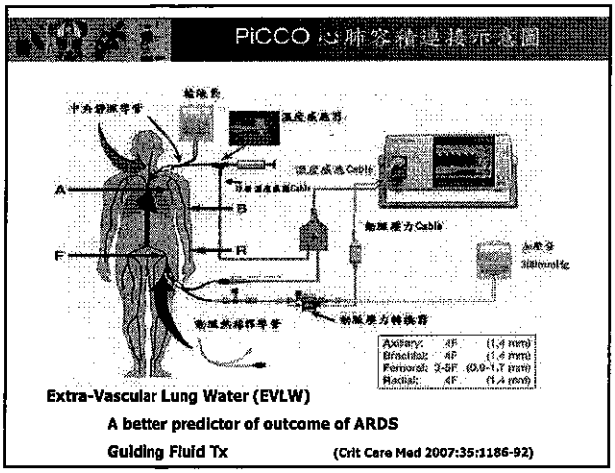


(Crit Care Research & Practice 2012; ID 952168)

Diagnostic Tools (2)

- Bronchoalevolar lavage
  - Improve targeting of antimicrobial Tx.
  - DDx for eosinophilic (eosinophils) & hypersensitive pnuemonitis (lymphocytes)
- Hemodynamic monitoring
  - Pulmonary artery catheter: no evidence
  - PiCCO (pulse continuous cardiac output)
  - Echocardiography: for heart function

(Postgrad Med J 2011; 87:612-22)



Extra-Vascular Lung Water (EVLW)

A better predictor of outcome of ARDS

Guiding Fluid Tx **(Crit Care Med 2007:35:1186-92)**

Diagnostic Tools (3)

- Biomarkers
  - Various inflammatory mediators ?
    - IL-6; IL-8, TNF receptor-1, von Willebrad factor (VWF), surfactant D (SP-D), intracellualr adhesion molecule-1 (ICAM-1), protein C, plasminogen activator inhibitor-1 (PAI-1)
    - Plasma IL-8 + SP-D: better predictors
  - Brain natriuretic peptide (BNP)
    - Low levels help exclude cardiogenic edema

(Postgrad Med J 2011; 87:612-22)

Treatment for ARDS

Hi Ref.

Directions of Tx. for ARDS

- Treat underlying diseases
  - Inhibition of inflammation
- Provide adequate oxygenation
  - Lung Protective Ventilatory Strategies
  - Hemodynamic support
- Adequate general supportive Tx:
  - Infection control, Early enteral nutrition, Stress ulcer prophylaxis
- Speed lung healing: Stem cell Tx

Adequate Oxygenation for ARDS

- Lung protective strategies
  - MV with low VT and limited airway pressure to reduce VILI from overdistension
  - Medium to high PEEP to keep alveoli open throughout the ventilatory cycle and reduce FiO_2
- Rescue Tx.:
  - Prone position, Airway pressure release ventilation, High frequency ventilation, ECMO

Selective Clinical Trails of ARDS (1)

Intervention	Reference	Study phase	Study population[a]	Results
Lung-protective ventilation	96	Phase III	ARDS (N = 53)	Decrease in mortality
Lung-protective ventilation	97	Phase III	ARDS (N = 861)	Decrease in mortality
Lung-protective ventilation	98	Phase II	ARDS (N = 103)	Decrease in mortality
High PEEP	108	Phase III	ARDS (N = 549)	No difference in mortality
High PEEP	109	Phase III	ARDS (N = 385)	No difference in mortality
High PEEP	110	Phase III	ARDS (N = 382)	No difference in mortality
High-frequency ventilation	116	Phase II	ARDS (N = 148)	No difference in mortality
Prone position	111	Phase III	ALI and ARDS in children (N = 102)	No difference in mortality
Prone position	112	Phase III	ARDS (N = 342)	No difference in mortality

(J Clin Invest 2012; 122:2731-40)

Meta-analysis

- Mortality

Group	*Odds Ratio(95%CI)*	*P value*
Low VT	0.75 (0.58-0.96)	0.02
High PEEP	0.86 (0.72-1.02)	0.08
VT & PEEP	0.38 (0.20-0.75)	0.005

- Use of rescue therapy

High PEEP	0.51 (0.36-0.71)	<0.001

(Ann Intern Med 2009;151:566)

Prone Positioning in Severe ARDS

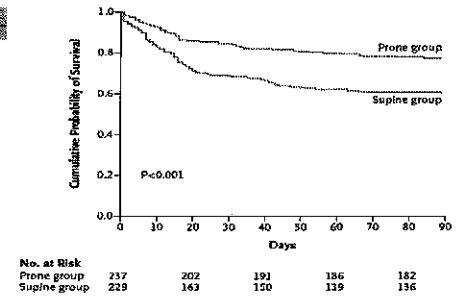


Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

(NEJM 2013; 368: 2159-2168)

Selective Clinical Trails of ARDS (2)

Neuromuscular blockade	113	Phase III	ARDS (N = 340)	Decrease in mortality
Esophageal pressure to adjust PEEP	114	Phase II	ARDS (N = 61)	Improved oxygenation
Surfactant	125	Phase III	ARDS (N = 448)	No difference in mortality
Methylprednisolone	126	Phase III	ARDS (N = 90)	No difference in mortality
Methylprednisolone	127	Phase III	ARDS (n = 24)	Decrease in mortality, but small study
Methylprednisolone	128	Phase III	ARDS (n = 180)	No difference in mortality
Methylprednisolone	129	Phase III	ARDS (N = 91)	Reduction in duration of mechanical ventilation, but major limitations related to study design

(J Clin Invest 2012; 122:2731-40)

Early Neuromuscular Blocker Improved Survival of ARDS

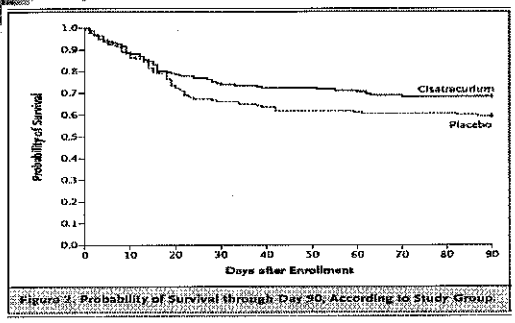
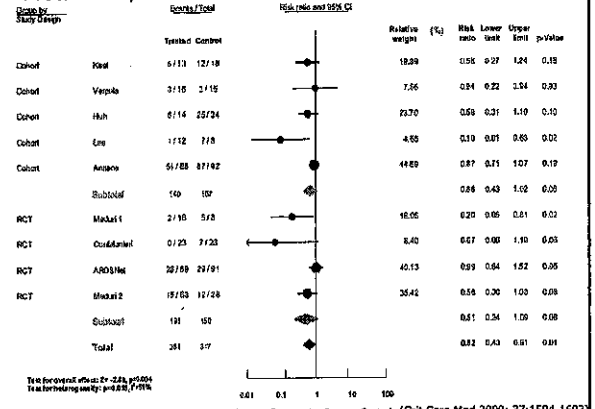


Figure 2. Probability of Survival through Day 90, According to Study Group.

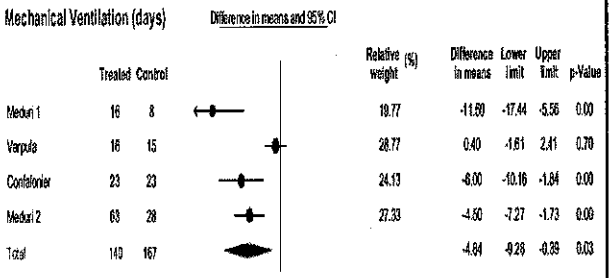
(NEJM 2010; 363:1107-1116)

Meta Analysis: Low Dose Steroid Decreases Mortality



(Crit Care Med 2009; 37:1594-1603)

Meta Analysis: Low Dose Steroid Decreases MV days



(Crit Care Med 2009; 37:1594-1603)

Selective Clinical Trails of ARDS (3)

Liposomal prostaglandin E_1	130	Phase III	ARDS (N = 356)	No difference in mortality for results
Antioxidants	132	Phase II	ARDS (N = 45)	No difference in mortality
Nitric oxide	135	Phase III	ARDS (N = 385)	No difference in mortality
β_2-Agonist (aerosolized)	136	Phase III	ARDS (N = 282)	No difference in mortality
β_2-Agonist (intravenous)	137	Phase III	ARDS (N = 330)	No difference in mortality
ω-3 Fatty acid supplement	138	Phase III	ARDS (N = 272)	No difference in mortality
Pulmonary artery versus central venous catheter	121	Phase III	ARDS (N = 1,000)	No difference in mortality

(J Clin Invest 2012; 122:2731-40)

Selective Clinical Trails of ARDS (4)

Fluid-conservative versus fluid-liberal therapy	129	Phase III	ARDS (N = 1,000)	More ventilator-free days with fluid-conservative therapy
Extracorporeal membrane oxygenation	115	Phase III	ARDS (N = 90)	Decrease in mortality, but results not conclusive
APC	134	Phase III	Nonseptic ARDS (N = 75)	No difference in mortality
APC	133	Phase III	Sepsis (N = 1,697)	No difference in mortality
GM-CSF	131	Phase II	ARDS (N = 139)	No difference in mortality

(J Clin Invest 2012; 122:2731-40)

Conservative Fluid Management Decreases MV Days

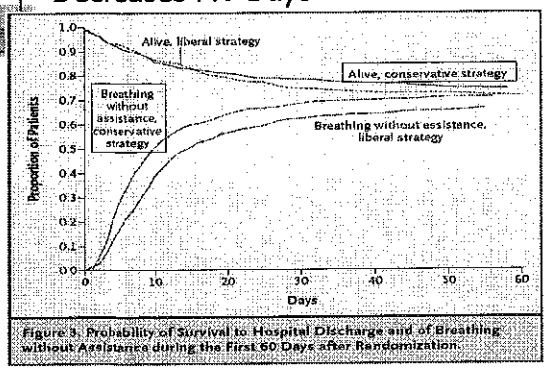
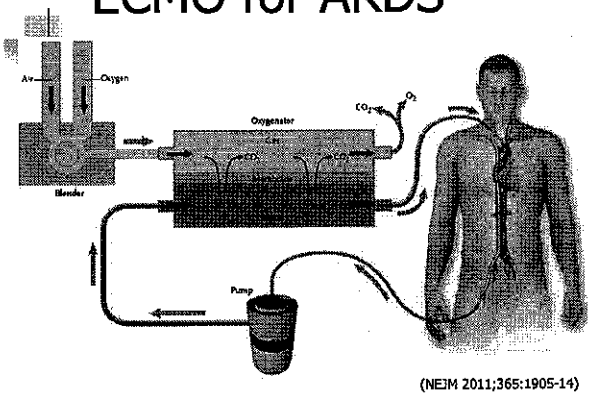


Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.

(NEJM 2006; 354:2564-75)

ECMO for ARDS



(NEJM 2011;365:1905-14)

CESAR: Transferring Severe ARDS to a ECMO Center Improved Survival

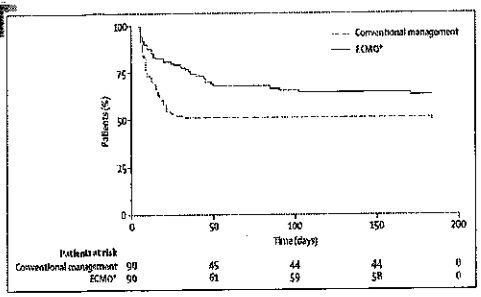


Figure 2: Kaplan-Meier survival estimates
ECMO=extracorporeal membrane oxygenation. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment. (22 No ECMO)

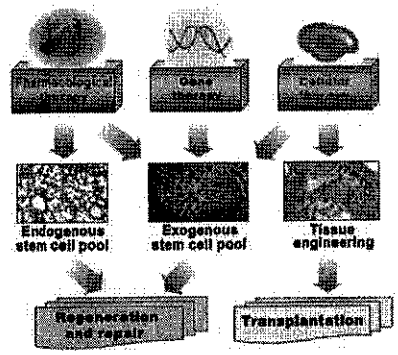
(Lancet 2009; 374:1351-63)

ECMO for Severe ARDS

- Major technological improvements in ECMO & the positive results of CESAR trial reignited the interest
- Successfully used as a rescue therapy for ARDS associated influenza A(H1N1)
- Precise indications for VV-ECMO remain controversial
- New trials for severe ARDS are needed

(Curr Opin Crit Care 2012; 18:527-532)

Future Direction: Stem Cell Therapies



(Eur J Clin Invest 2006;36:310-319)

Intratracheal Tx with MSC Improved Survival in The LPS Model of ALI

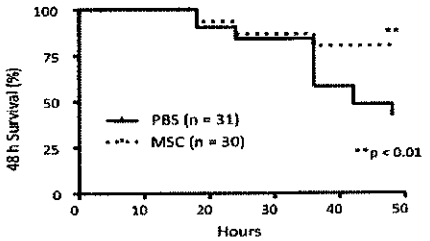
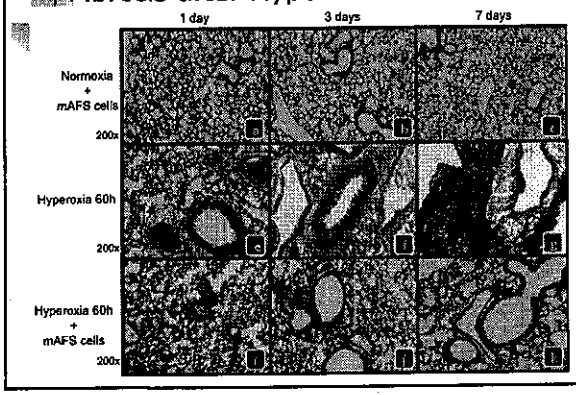


FIGURE 2. Intratracheal treatment with mouse MSC improved survival at 48 h in an endotoxin model of acute lung injury in mice. MSC or PBS was administered intratracheally (IT) 4 h after IT instillation of endotoxin (5 mg/kg). Forty-eight hour survival was 80% in MSC group vs 42% in PBS group (n = 30 for MSC group, n = 31 for PBS group, $^{**}P < .01$ using a log-rank test). MSC = mesenchymal stem cells; PBS = phosphate-buffered saline. (Reprinted with permission from Gupta et al.[16])

(Chest 2010; 138:965-972)

Our Studies: Stem Cells Reduce Lung Fibrosis after Hyperoxia



Aerosolized EC-SOD Prevents Hyperoxic Lung Injury

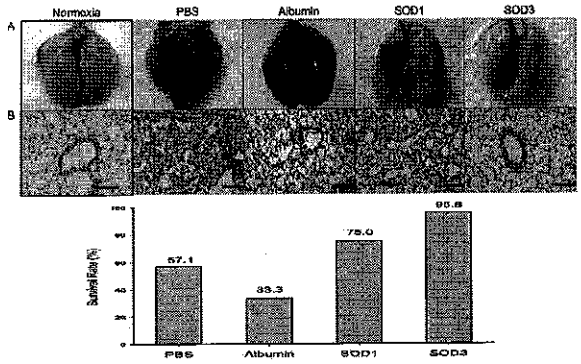


Figure 3. Effects of aerosolized CuZn-SOD and rhEC-SOD on survival after 72 h of hyperoxia. Phosphate-buffered saline (PBS)

(PLoS One 2011: 6: e26870)

Take Home Messages

Berlin Definition of ARDS

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild (No ALI)	200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

(JAMA 2012; 307:2526-33)

Management for ARDS

- Early recognition and avoidance of risk factors
- Initial intervention
  - Lung protective ventilation
  - Conservative fluid management
- Tx for life-threatening hypoxemia => check Pplat
  - Pplat < 30 => Recruitment and/or High PEEP alone
  - Pplat > 30 => Prone position or HFV
  - No improvement => Inhaled NO
  - Low dose steroid after evaluation
  - ECMO

(Crit Care Med 2010; 38:1644-1650)

New Strategies for ARDS

- Recommended
  - Airway Pressure Release Ventilation (APRV)
  - High Frequency Ventilation (HFV)
  - Extracorporeal Membrane Oxygenation (ECMO)
- Controversial
  - Prone positioning
  - Surfactant
  - Paralysis
- Negative
  - Nitric oxide
  - Perflubron

(MacIntyre, 2013-7-18)

Thanks for Your Attention