The Acute Respiratory Distress Syndrome

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ARDS: Incidence/Mortality

1.5 - 7.5 cases/100,000 pop./yr

(~150,000 cases U.S./ yr.)

~ 50% mortality

~ 75,000 deaths U.S./yr.

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Criteria for ARDS

Acute onset

Relative hypoxia (PaO_2/FiO_2 less than 200)

Bilateral infiltrates on CXR

No signs of LV failure (PCWP less than 18)

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The JAMA Network

From: **Acute Respiratory Distress Syndrome: The Berlin Definition**
JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
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	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

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

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Direct Lung Injury	Indirect Lung Injury
Common causes	**Common causes**
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple transfusions
Less common causes	**Less common causes**
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

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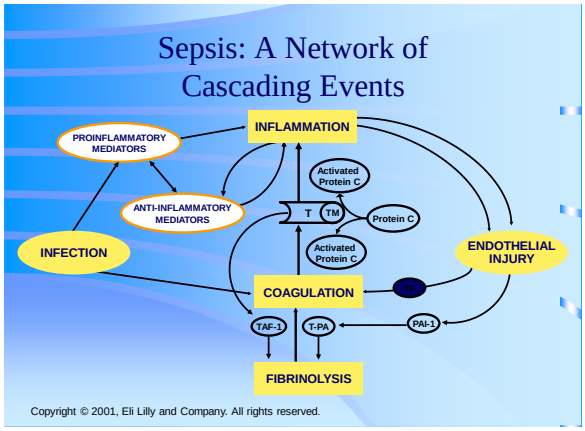
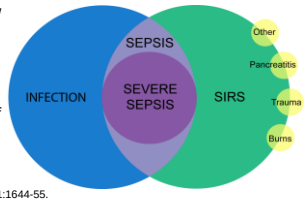


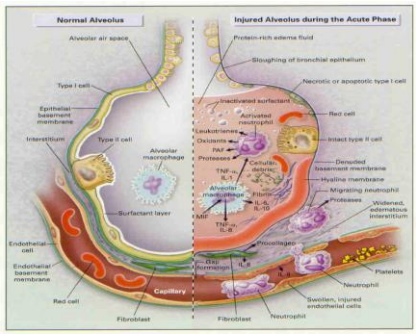
Sepsis: A Complex Disease

This Venn diagram provides a conceptual framework to view the relationships between various components of sepsis.

The inflammatory changes of sepsis are tightly linked to disturbed hemostasis.



Adapted from: Bone RC et al. *Chest.* 1992;101:1644-55.
Opal SM et al. *Crit Care Med*. 2000;28:S81-2.



ARDS: Treatment

Preventive care

"Supportive care"

Lung protective strategies

- **Alternate modes of mechanical ventilation (APRV, HFOV)**
- **ECMO**

Therapeutic paralysis

Prone positioning

Nitric Oxide

Immunomodulation, Anti-oxidants, Surfactant

ARDS: Supportive Care

Delivery of care in the ICU

Supplemental oxygen

Mechanical ventilation (PEEP)

Assure adequate sedation

Avoidance of fluid overload

Prevention of complications (i.e gastrointestinal bleeding, DVT, etc.)

Comparison of Two Fluid-Management Strategies in Acute Lung Injury (FACTT Trial)

Conservative vs liberal fluid strategy of fluid management in ARDS

Fluid balance over 7 days -136 mLs in conservative group and + 7.0 L in liberal group

Conservative group had increased oxygenation index, 2 day shorter length of ventilation and time in ICU. No difference in mortality

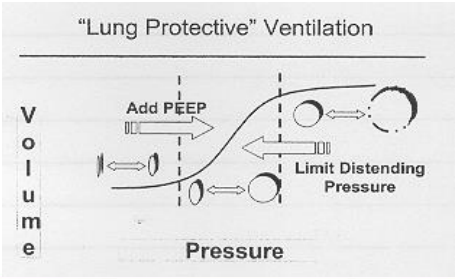
- N Engl J Med 2006 354:24:2564-2575

Mechanical Ventilation: Goals in ARDS

Assure adequate oxygen delivery

Avoid toxicity (barotrauma/oxygen)

Preventing overdistetion and under-recruitment injury



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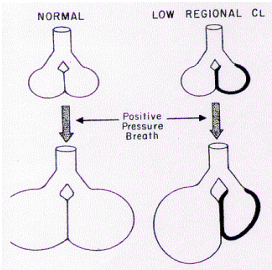
Overdistention may be regional
Even a "normal" VT can create regional overdistention



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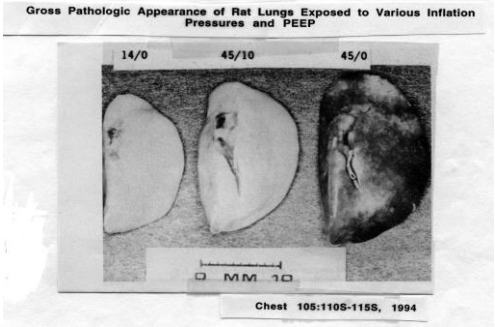

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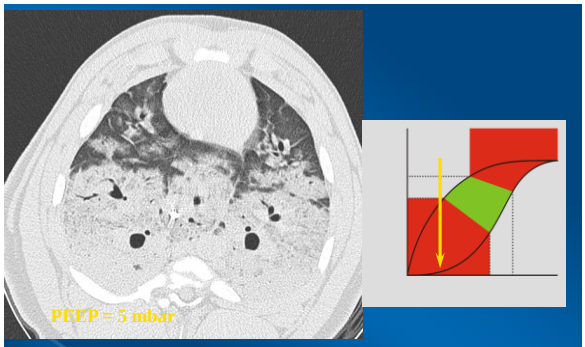

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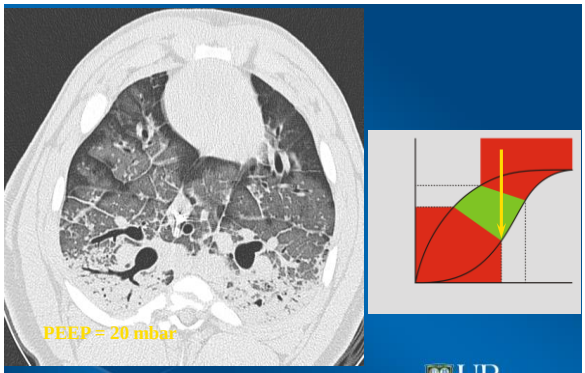

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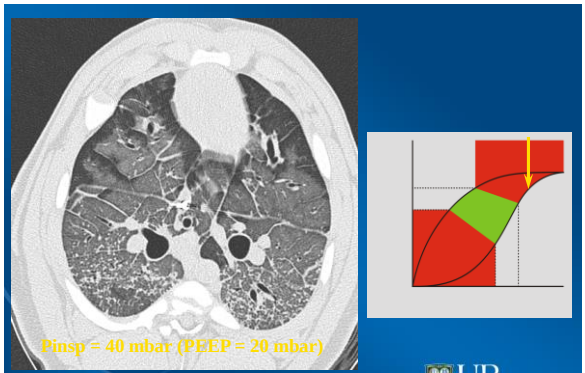

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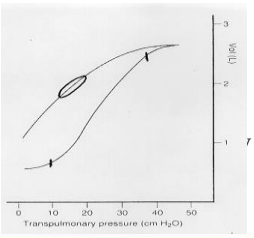
Overdistention/ underrecruitment

PV curve:



Physical lung damage from both:

- overstretch (nl <35)
- collapse/open

Systemic cytokine release - other organ system injuries

Oxygen Toxicity

Time and dose dependent

Mediated by oxygen radicals

Inflammation, hyalinization, edema

Keep FiO2 ≤ 60%

Permissive Hypercapnia

Deliberate attempt to limit ventilator induced lung injury

Limits tidal volume (alveolar ventilation)

Results in elevated $PaCO_2$

Has been utilized in ARDS and status asthmaticus

Well tolerated if occurs slowly

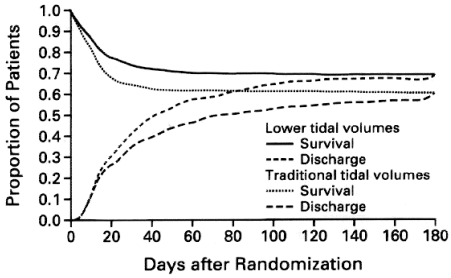
The NIH ARDS Network

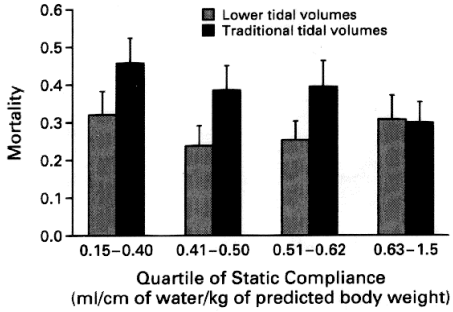
Prospective, randomized study comparing traditional (12 ml/kg) vs low (6 ml/kg) tidal volumes in ARDS

Stopped after enrollment of 861 patients

Mortality 40% in traditional TV group vs 31% in the low TV group

- **NEJM 342:1301-8, 2000.**





Current Guidelines for Ventilatory Support in ARDS

Based on concept of lungs being "small" rather than "stiff"

Limit transalveolar pressure to 30 cm H_2O (TV 5-8 ml/kg)

PEEP 7 - 20 cm H_2O

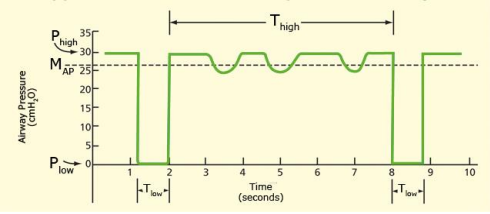
Limit FiO2 to lowest tolerable

Oxygenation Index (OI)

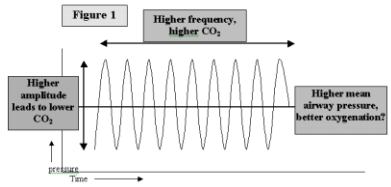
$$OI = FiO2 \times MAP$$

(All modes of ventilation are variations of how airway pressure is applied)

Airway Pressure Release Ventilation



High Frequency Oscillatory Ventilation



High Frequency Oscillation in Early Acute Respiratory Failure

Randomized trial in 39 ICUs

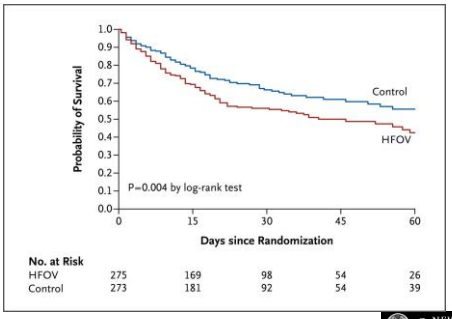
HFOV vs LTVV in early moderate to severe ARDS (less than 72 hours)

Trial stopped early after 548 patients

In hospital mortality 47% in HFOV vs 35% in LTVV (p = 0.005)

In adults with moderate to severe ARDS early application of HFOV may increase in hospital mortality

- **Ferguson et al, N Engl J Med 368:795-805, 2013**



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Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

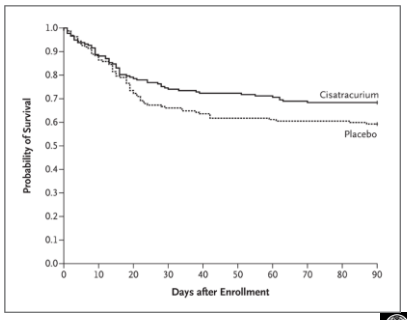
340 ICU patients with severe ARDS ≤ 48 hours, received 48 hours of study drug (P/F ≤ 150)

Cis-atracurium vs placebo

Adjusted 90 day mortality 32% in cis-atracurium group, 41% in placebo group

?Class effect or related to cis-atracurium

- **Papazian et al, N Engl J Med 363:1107-1116, 2010**



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Prone Positioning in ARDS

Improves oxygenation by improving V/Q matching to dorsal lung units

Improves drainage of dorsal lung units

Increases FRC

Not without risks

Recent study suggests reduced mortality in severe ARDS

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Prone Positioning in Severe Acute Respiratory Distress Syndrome

466 patients with severe ARDS (P/F less than 150) for less than 36 hours

Prone positioning for 16 hours vs supine

28 day mortality 16% prone vs 33% supine (p<0.001)

90 day mortality 24% prone vs 42% supine (p<0.001)

- Guerin et al, New Engl J Med 2013

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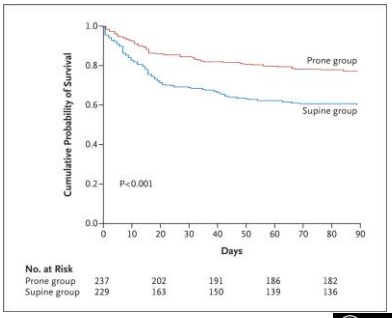

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ARDS: Salvage Therapy

Nitric oxide (Flolan)

ECMO

APRV

HFOV

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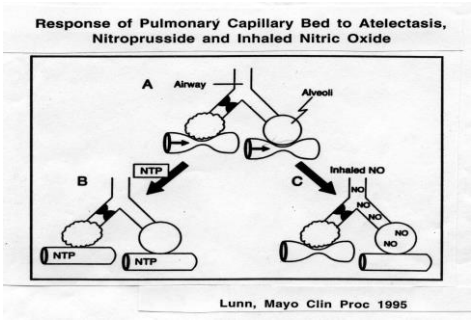
Nitric Oxide (INO) In ARDS

- NO is the endothelium-derived relaxing factor (EDRF)
- Vasodilator
- Improves V/Q matching
- Administered by inhalation
- Avoid the systemic effects of other vasodilators
- Very short half-life



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Effects of Inhaled Nitric Oxide in Patients with Acute Respiratory Distress Syndrome: Results of a Randomized Phase II Trial

- Prospective, multicenter, placebo-controlled study
- ARDS patients enrolled within 72 hrs of onset of the disease
- Randomized to placebo, 1.25, 5, 20, 40 or 80 ppm INO
- No difference in mortality
- Trends toward benefit of INO 5PPM group
  - CCM 26:15-23, 1998

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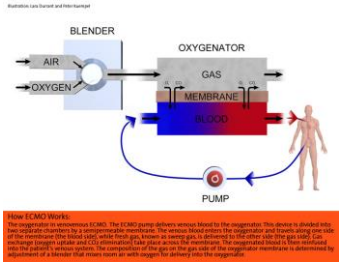
Extracorporeal Membrane Oxygenation (ECMO)



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Efficacy and Economic Assessment of Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult respiratory Failure (CESAR): A Multicenter Randomised Trial

- 180 adults with ARDS randomized to continued ventilator mgt or referral to ECMO center with severe respiratory failure (75% of received ECMO)
- 63% of transferred patients vs 47% conventially treated patients survived 60 days without severe disability
- Unclear if effect due to larger center or ECMO itself
  - Peek et al, Lancet 374:1351-1363, 2009

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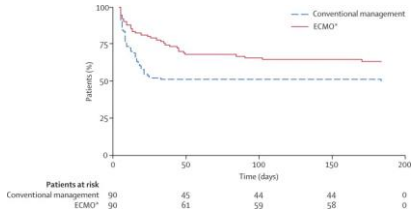

Figure 2 Kaplan-Meier survival estimates ECMO=extracorporeal membrane oxygenation. *Patients were randomly allocated to consideration for treatment by ECMO, but did not necessarily receive this treatment.

Giles J Peek , Miranda Mugford , Ravindranath Tiruvoipati , Andrew Wilson , Elizabeth Allen , Mariamma M Thalanany...

Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

The Lancet, Volume 374, Issue 9698, 2009, 1351 - 1363

http://dx.doi.org/10.1016/S0140-6736(09)61069-2

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ARDS: Limiting the Immune Response

Methylprednisolone ineffective in preventing or treating acute phase of ARDS

Anecdotal reports of success with steroids in the fibroproliferative phase of ARDS

ARDS: Limiting the Immune Response

Plethora of immunomodulators have been studied (Anti-TNF abs, IL-1 ra, and IL-8 abs, anti CD18 abs, ibuprofen, ketoconazole etc.)

ARDS: Prognosis

Due to the heterogeneity of the disease, exact mortality rates are unknown

~ 40-50% mortality rate generally quoted

Risk factors include increased age, sepsis, multiple organ dysfunction, acidosis

Majority of deaths due to multiple organ failure or sepsis not to respiratory failure

Lung function generally recovers completely although some develop fibrotic residua

Survivors have functional disability, weakness and muscle wasting 1 year after discharge

ARDS: Conclusions

ARDS is a heterogenous disease with both direct and indirect causes

ARDS and SIRS are closely linked

Lung protective strategies based on the concept of the lung being "small" rather than "stiff"

Limiting fluids in hemodynamically stable patients may be advantageous

ARDS: Conclusions

Prone positioning and therapeutic paralysis may improve outcomes in severe cases

Which salvage modes/therapies to use remains up for debate

New focus on long term outcomes as well (role of early mobility?)

Probably no "magic bullet"

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