ARDS and treatment strategies

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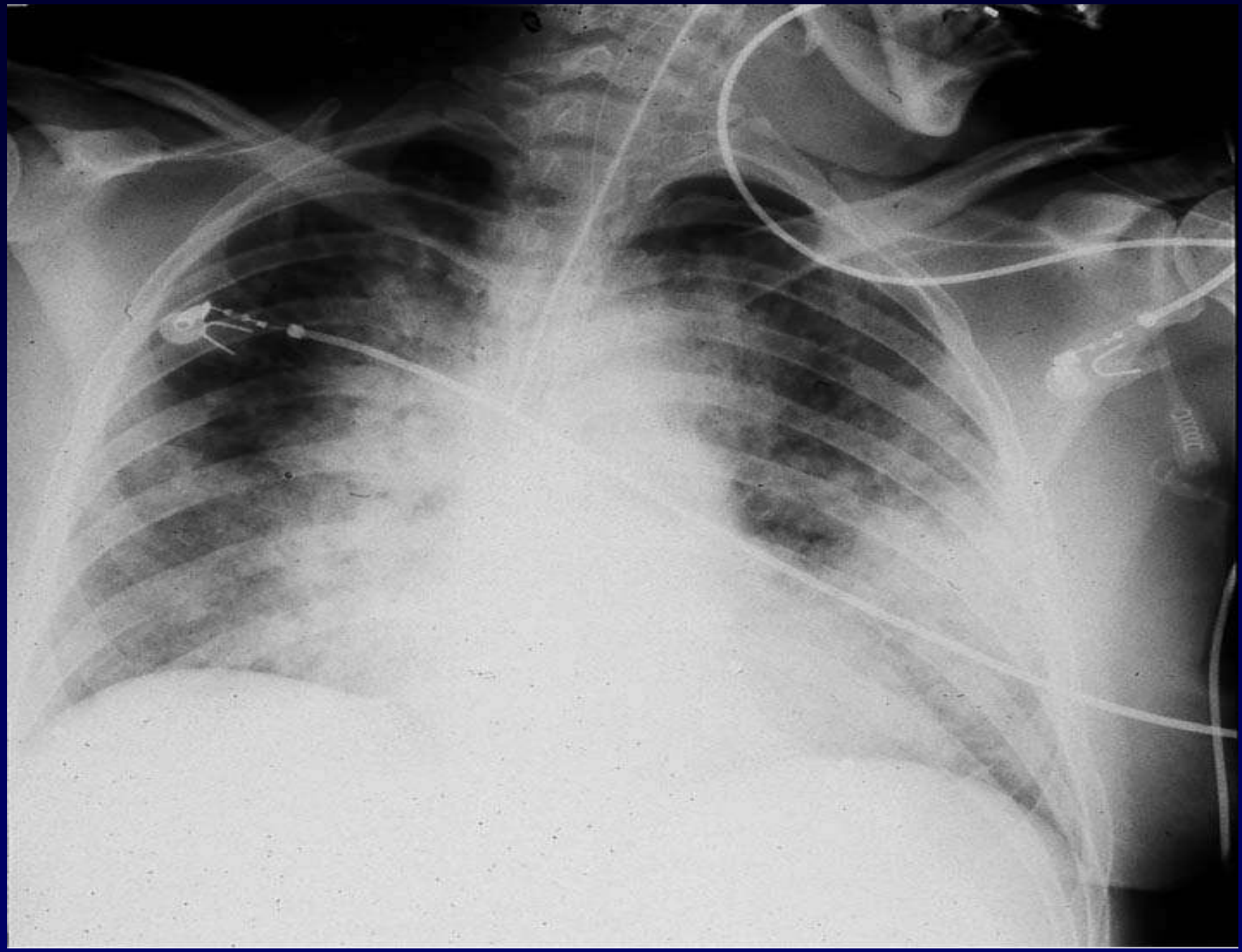


ARDS: Definitions

- History of predisposing condition
- Refractory hypoxaemia of acute onset
  - PaO_2/FiO_2 ratio:
    - <40 ALI
    - <27 ARDS
- Bilateral pulmonary infiltrates (CXR)
- Absence of left ventricular dysfunction

American-European Consensus Conference on ARDS

Am . J. Resp. Crit. Care Med. 1994 **149:** 818

ARDS: Definitions

- The 1994 American-European Consensus Conference (AECC) definition has considerable issues regarding reliability and validity…..

ARDS: the Berlin Definition

- Using a consensus process, a panel of experts convened in 2011 (EISCM, ATS and SCCM) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance.
- Marco Ranieri, Gordon D. Rubenfeld, B. Taylor Thompson, Niall D. Ferguson, Ellen Caldwell, Eddy Fan, Luigi Camporota, and Arthur S. Slutsky,

ARDS: the Berlin Definition

- Proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia:
  - mild (PaO_2/FIO_2 200 - 300 mm Hg),
  - moderate (PaO_2/FIO_2 100 - 200 mm Hg),
  - severe ($PaO_2/FIO_2 \leq 100$ mm Hg)
- and 4 ancillary variables for severe ARDS: radiographic severity,
  - respiratory system compliance ($\leq$40 mL/cm H_2O),
  - positive end-expiratory pressure ($\geq$10 cm H_2O),
  - corrected expired volume per minute ($\geq$10 L/min).

ARDS: the Berlin Definition

- The draft Berlin Definition was evaluated using meta-analysis of 4188 patients with ARDS from 4 multicenter trials and 269 patients with ARDS from 3 single-centre data sets.
- The 4 ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition.

ARDS: the Berlin Definition

Severity related to outcome:

- Mortality
  - Mild - 27%; (CI, 24%-30%)
  - Moderate - 32%; (CI, 29%-34%)
  - Severe - 45%; (CI, 42%-48%), ($P < .001$)
- Duration of mechanical ventilation in survivors
  - Mild - 5 days [IQR], 2-11;
  - Moderate - 7 days [IQR, 4-14]
  - Severe - 9 days [IQR, 5-17] ($P < .001$).
- Predictive value for mortality improved:
  - Berlin Definition area under the receiver operating curve of 0.577 (95% CI, 0.561-0.593)
  - AECC 0.536 (95% CI, 0.520-0.553; $P < .001$).

JAMA. 2012;():1-8. doi:10.1001/jama.2012.5669

Still some problems

- Too broad a church
- What is acute?
- Role of CXR?
- What of inflammation?
- What of heart failure?
- Epidemiological or clinical?

Ferguson, 2004; 2006

Lets just do those sums…

PaO_2 of 10 kPa	PaO_2/FiO_2 ratio	
– FiO_2 of 0.8 (80% oxygen)	12.5	ARDS
– FiO_2 of 0.6 (60% oxygen)	16.7	ARDS
– FiO_2 of 0.4 (40% oxygen)	25	ARDS
– FiO_2 of 0.3 (30% oxygen)	33.3	ARDS
– FiO_2 of 0.26 (26% oxygen)	38.5	ARDS
– FiO_2 of 0.21 (air)	47.6	normal

Bernard et al. The American-European consensus conference on ARDS.
Am J Respir Crit Care Med 1994

ARDS: Treatment

ARDS: Treatment

- Oxygen therapy
- Treat cause
- Organ support
  - respiratory NIPPV/IPPV
  - cardiac myocardial depression/sepsis
- Other treatments
  - Ventilatory strategies, Oscillator, ECMO, Novolung, Paralysis, Steroids Nitric Oxide, [Statins, Interferon-β, Heliox, Surfactant, Antioxidants, immunomodulation..]
- Avoid mistakes

Controversies in Management

- What oxygen level?
- Which ventilation mode?
- What PEEP?
- When to CT?
- Rescue therapies: inverse ratio, prone, NO, >30 cmH_20, oscillation, ECMO etc.
- What CO_2?
- Fluid management?
- What Hb?
- Drugs: neuromuscular blockers, steriods, sildenafil, interferon-beta, statins, $beta_2$ agonists, surfactant, …
- What mode to wean?
- When to tracheostamise?
- Future – oxygen / CO_2 removal and negative pressure ventilation?

The New England
Journal of Medicine

VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

- 20 medical centres 1996 - 1999, stopped after 3 years n=861 (proposed 1600).
- Compared TV 12ml/kg (plateau <50cmH_2O) versus TV 6ml/kg (plateau < 30cm H_2O).
- Relative reduction in mortality of 22% (absolute 9%: 31 vs 39.8%)

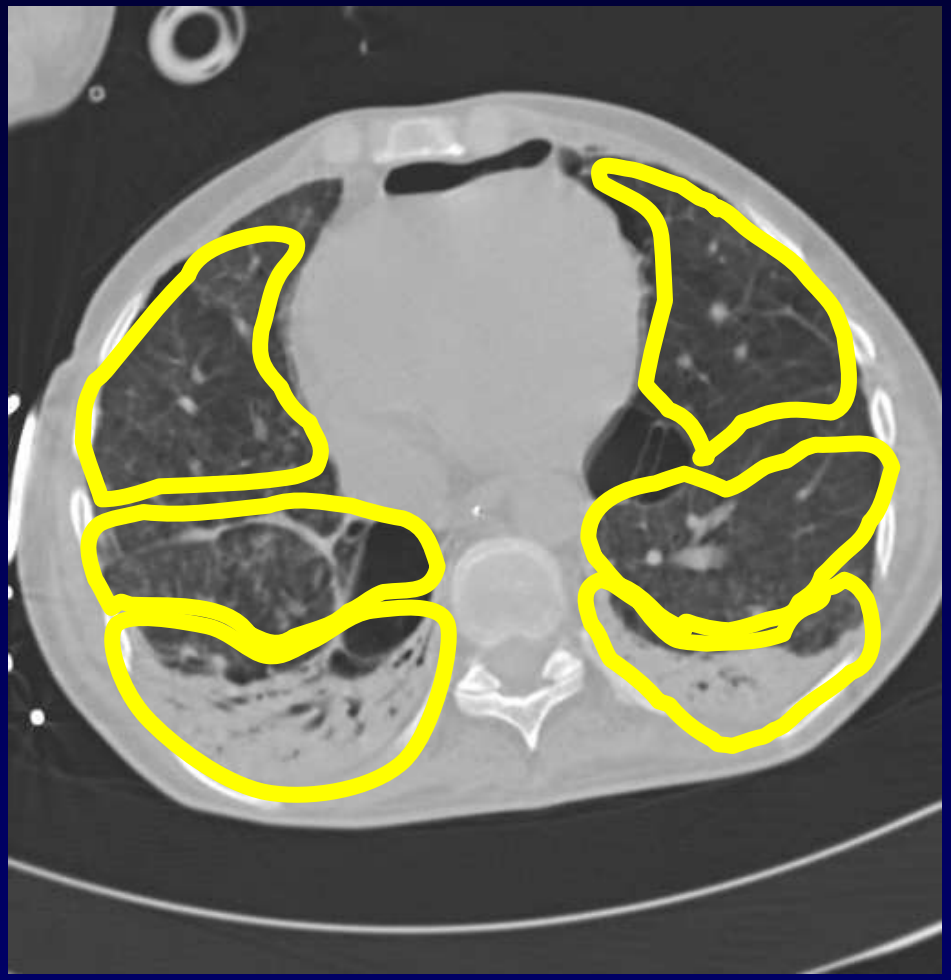
Problems (1)

- Unethical(?) exposure of controls to excess TV
- Not clear whether reduction in TV or reduction in plateau pressure or hypercapnic acidosis that conveys benefits
- Very wide scatter of TV and plateau pressure before trial entry
- Patients excluded from trial had significantly lower mortality than controls
  (Ferguson, 2005; Deans, 2005)

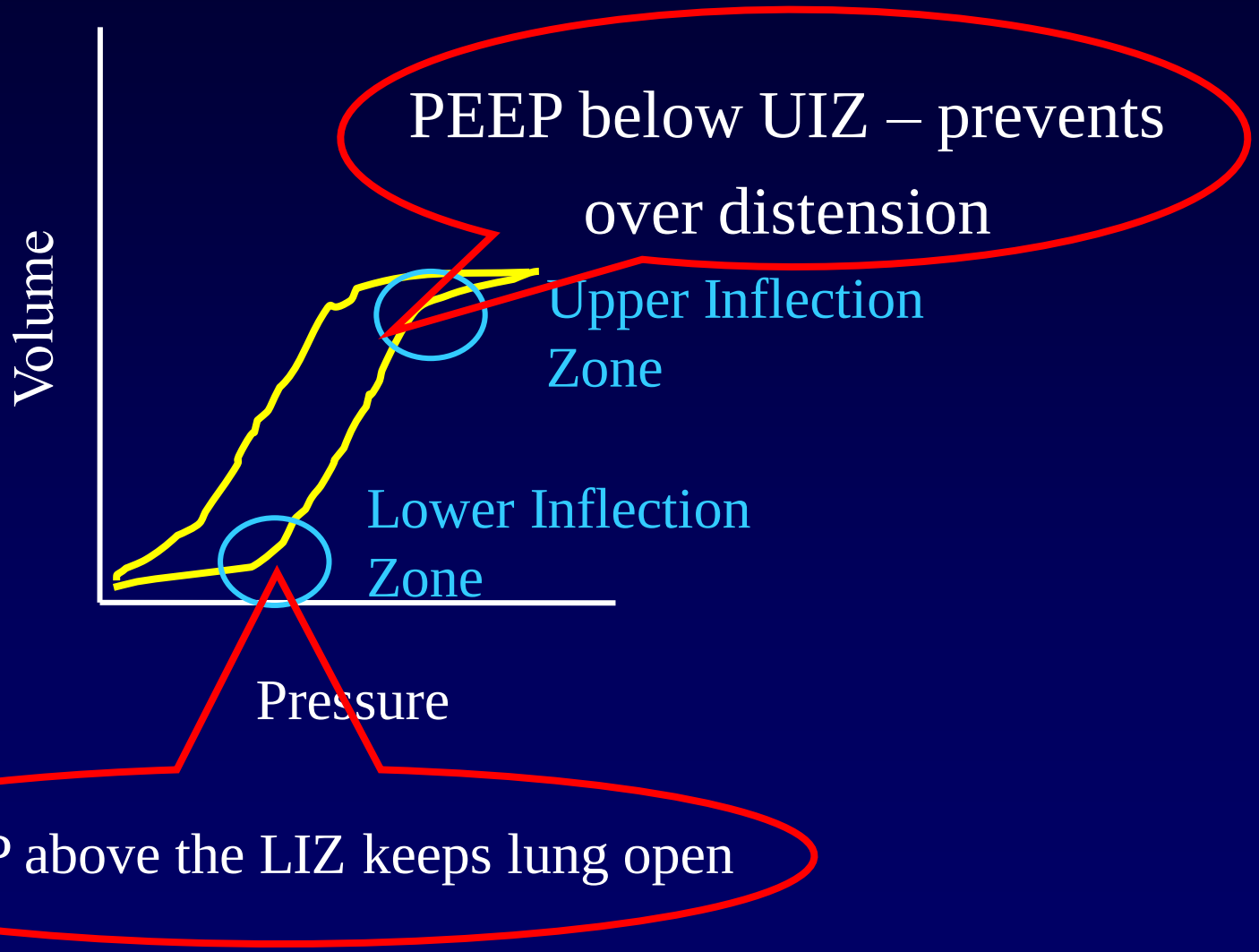

DELTA
Delta
Air Lines

ARDS: Ventilatory protocol

The Baby Lung concept



PEEP and PV curves



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 22, 2004 VOL. 351 NO. 4

Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*

High vs low PEEP: ALVEOLI trial

- 549 patients
- 6ml/kg TV, plateau pressure < 30 cm water
- Randomised to low or high PEEP.
- No difference in outcome.

Correct Level of PEEP: LOVE

Lung Open Ventilation Trial (Canada)

Primary endpoint: Hospital mortality

n=983, 30 centres
Inclusion: PF ratio <250

6 ml/kg VT

Plateau pressure <40 cm H_20 (LOVE)

Plateau pressure <30 cm H_20

Correct Level of PEEP: LOVE

Lung Open Ventilation Trial (Canada)

LOVE group developed **less** refractory hypoxaemia and had less ‘rescue’ therapies

No change in primary endpoint

Concluded that strategy was **safe**

Correct Level of PEEP: Express

Prospective RCT, 37 French ICUs

Primary endpoint: Death at 28 days

Inclusion: PF ratio <300

6 ml/kg VT

'Minimal distension' – PEEP 5-9 cm H_20

'Maximal recruitment' – PEEP increased to achieve plateau pressure 28-30 cm H_20

Correct Level of PEEP: Express

Improved oxygenation in the high PEEP group

Increased ventilator-free days and organ supported days in high PEEP group

No change in primary or secondary endpoints


BILLS

Correct Level of PEEP: Express

Subgroup analysis

In most hypoxic patients at start of trial
there was improved mortality in the high PEEP group

??High PEEP in targeted groups??

High Frequency Oscillation (HFO)

- Oscar Trial – HTA funded UK mechanical ventilation trial
- normal 6 mls/kg <30 cm H20 vs High Frequency Oscillation
- Recruitment closed. @800 patients. Results November

Prone Ventilation

- Proseva Study
- not yet published but presented at EISCM congress.
- Fascinating French multi-centre (and one Spanish centre) study of proning for ≥16 hrs/day in severe ARDS. 450-odd patients and a halving in mortality (from approx 31% to 16%).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

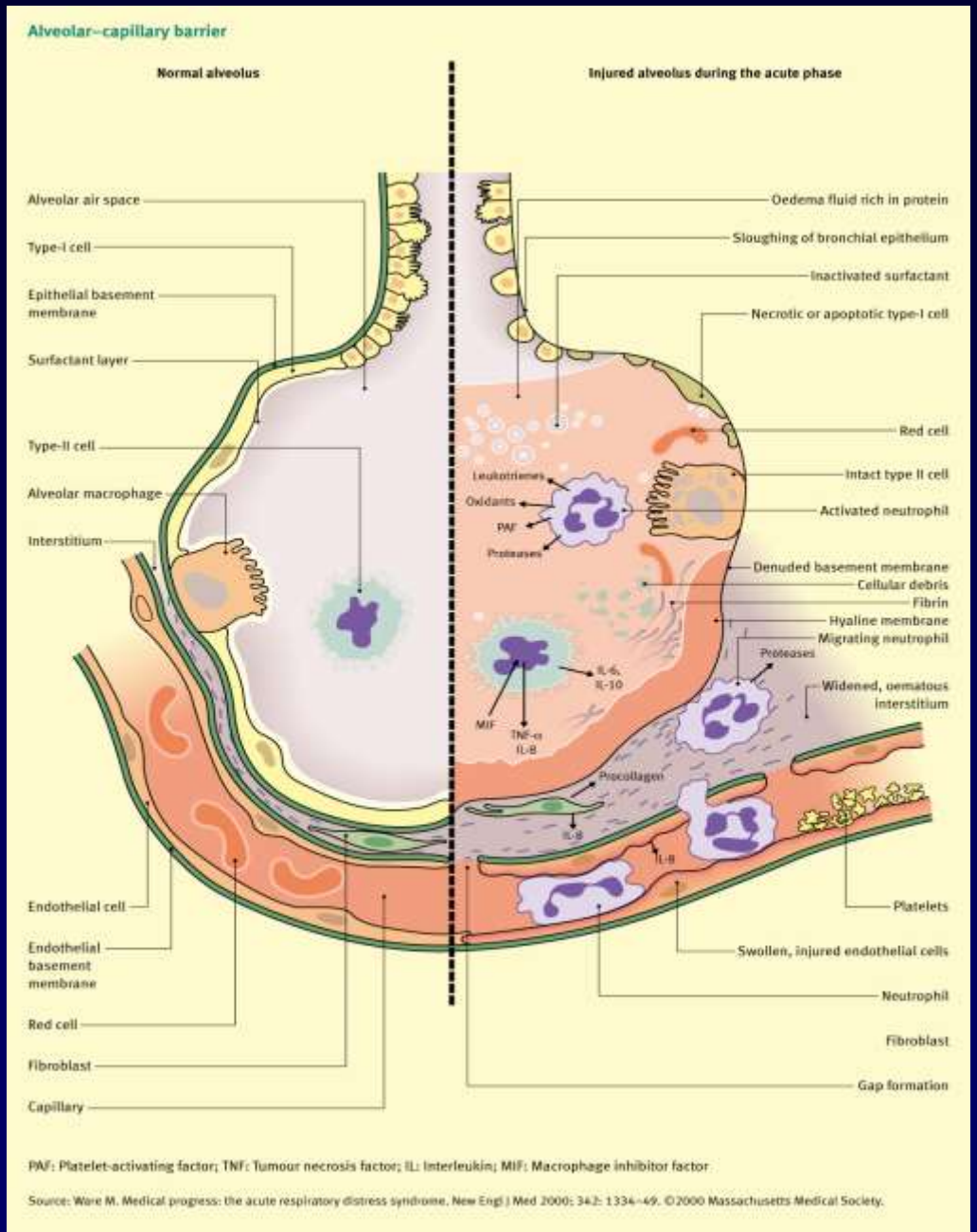
The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

LET'S HAVE ONE MORE
AND THEN WE'LL GO !!

Comparison of two fluid-management strategies

- Cumulative fluid balance during the first 7 days was:
  - 136+/-491 ml in the conservative group
  - 6992+/-502 ml in the liberal group ($P<0.001$).
- During first 28 days conservative strategy improved:
  - Oxygenation index [mean airway pressure x FiO_2/PaO_2 x 100]
  - Lung injury score
  - Ventilator-free days (14.6+/-0.5 vs. 12.1+/-0.5, $P<0.001$)
  - Days off ICU (13.4+/-0.4 vs. 11.2+/-0.4, $P<0.001$)
- Conservative group did not have any difference in:
  - Prevalence of shock
  - Use of dialysis

Pharmacological treatments????



PAF: Platelet-activating factor; TNF: Tumour necrosis factor; IL: Interleukin; MIF: Macrophage inhibitor factor

Source: Ware M. Medical progress: the acute respiratory distress syndrome. New Engl J Med 2000; 342: 1334–49. ©2000 Massachusetts Medical Society.

ARDS: successful treatments

- cisatracurium paralysis improves survival in early ARDS - ACURASYS trial . Papazian et al *NEJM*
- 340 patients - ARDS within 48 hours
- 90-day mortality 31.6% vs 40.7%, *P*=0.04.
- Confined to those with P/F ratio of <16.
- More ventilator-free time, less other organ failure
- Muscle weakness similar.

- May work by facilitating lung-protective ventilation.

ARDS: Steroids??

- No benefit in early ARDS
- Now no evidence it improves survival in late ARDS
  - It does speed extubation (more reintubations)
  - ? Increase CIPN
- No improvement or deterioration by 7 days
  - exclude infection
  - methylprednisolone 0.5 mg/kg QDS
  - reduce at 14 days and tail off from day 21 to 32
  - stop early (day 14) if non-responder

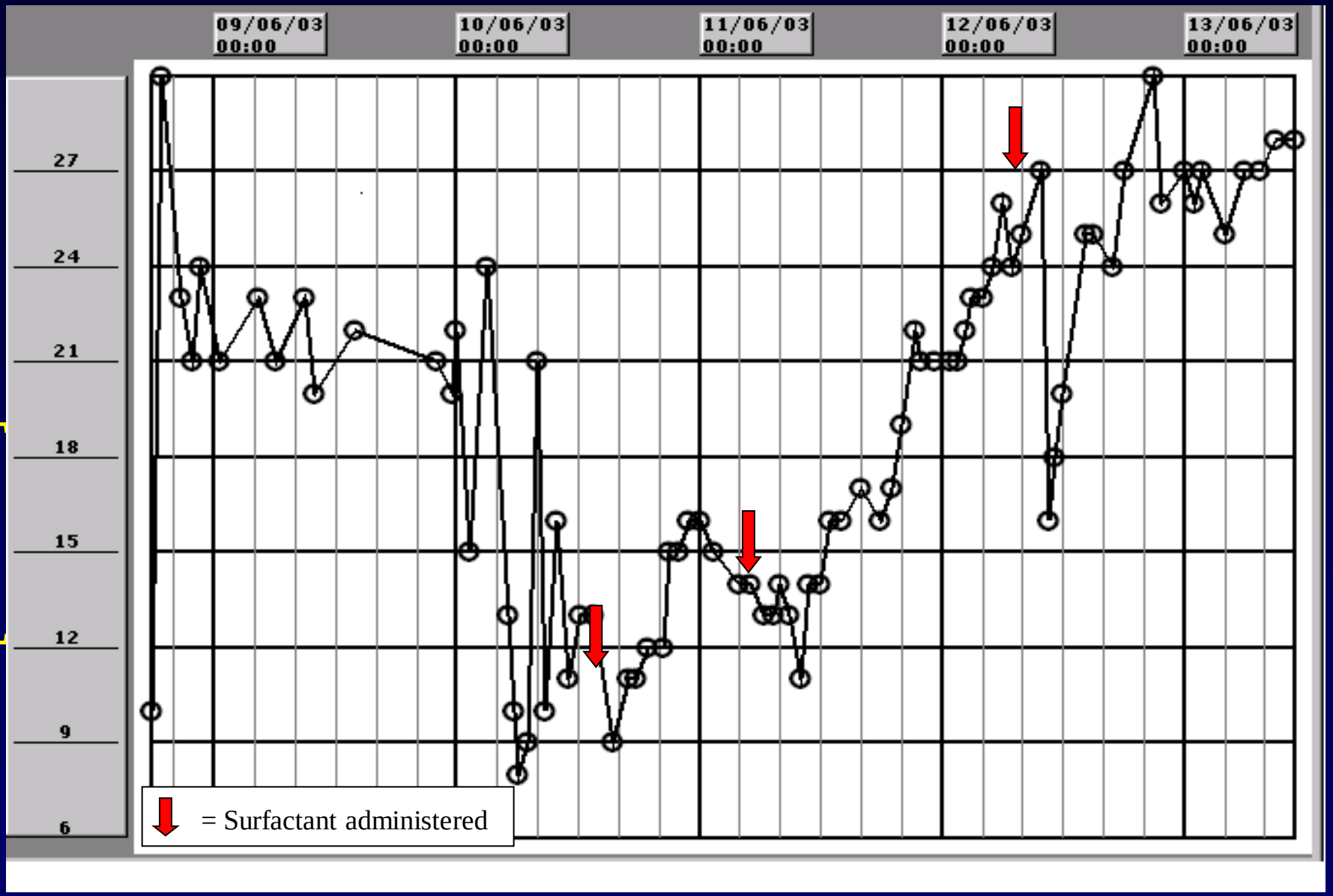
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

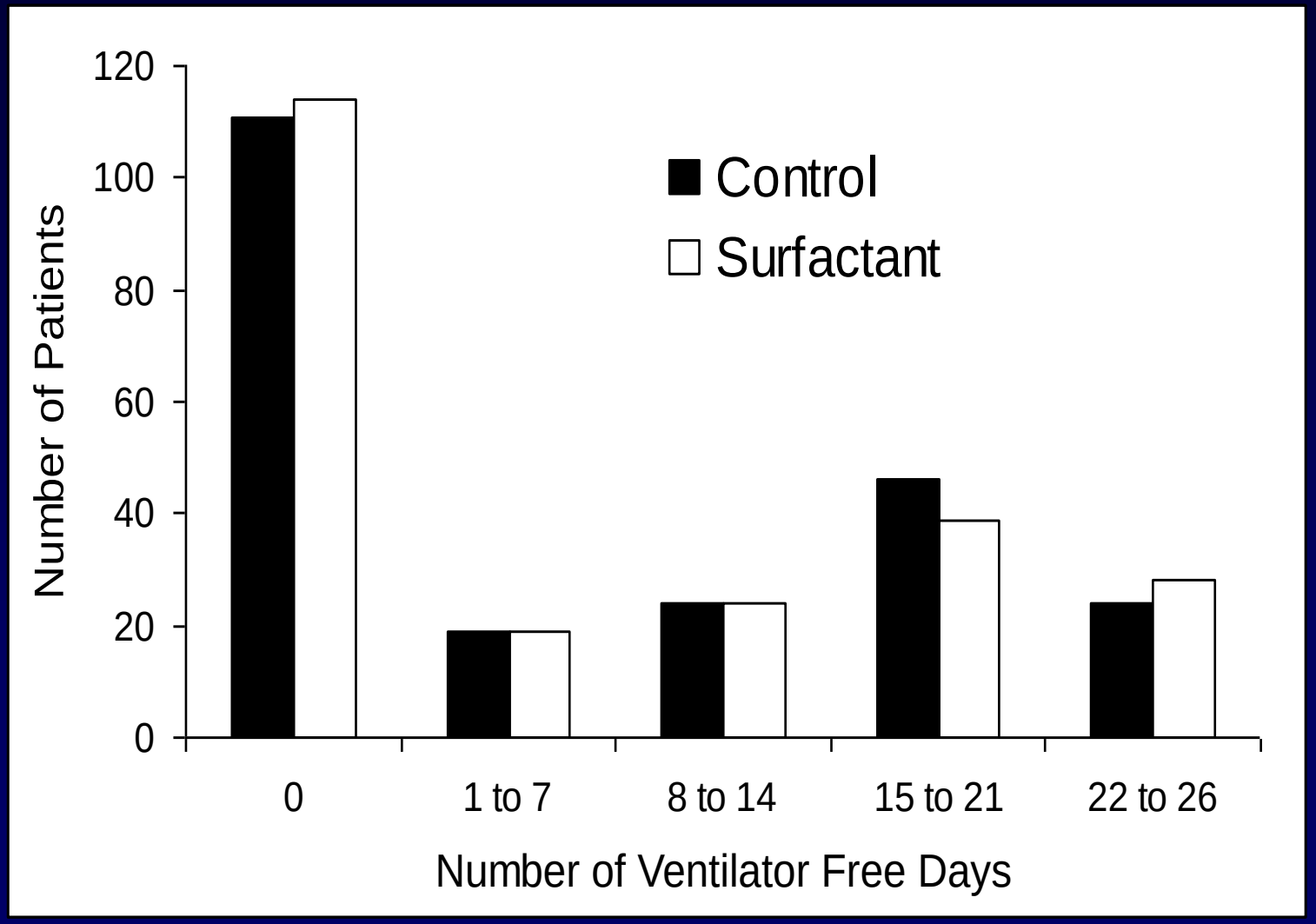
Effect of Recombinant Surfactant Protein C–Based Surfactant on the Acute Respiratory Distress Syndrome

Roger G. Spragg, M.D., James F. Lewis, M.D., Hans-Dieter Walmrath, M.D., Jay Johannigman, M.D., Geoff Bellingan, M.D., Pierre-Francois Laterre, M.D., Michael C. Witte, M.D., Guy A. Richards, M.D., Gerd Rippin, Ph.D., Frank Rathgeb, M.D., Dietrich Häfner, M.D., Friedemann J.H. Taut, M.D., and Werner Seeger, M.D.

$[PO_2/FiO_2]$ ratio / time



Venticute Surfactant Trial: Outcome *1)* Ventilator Free days



ARDS: other drugs

- Beta2 Agonists –BALTI 2 suspended
- Sildenafil – pulmonary hypertension and right heart failure
- *H*ydroxymethylglutaryl-CoA reductase inhibition with simvastatin in *A*cute lung injury to *R*educe *P*ulmonary dysfunction – The HARP-2 Trial
- Interferon Beta – Boosting endothelial CD73 and reducing lung leak – The Faron Trial

Pathogenesis

- Inflammation and vascular leak

How can we control the vascular leak and inflammation?

- Surfactant dysfunction

Failed

- Iatrogenic barotrauma driving further inflammation

In place: 6 mls/kg

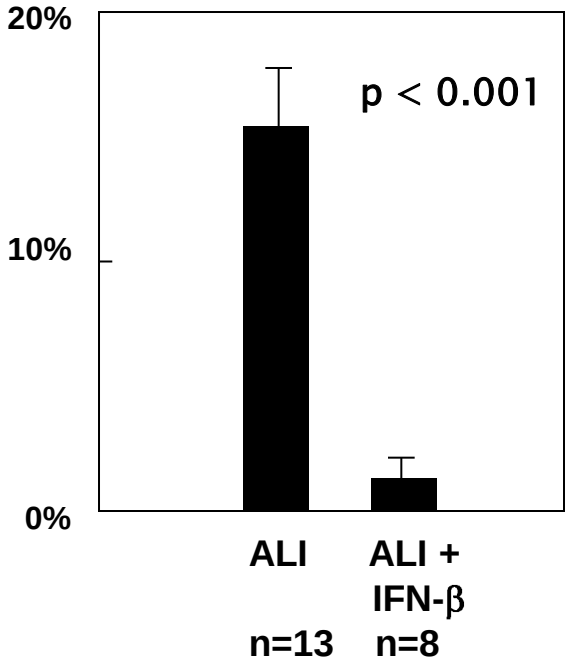
Post-ischemic IFN-beta treatment prevents leakage of vascular beds in ALI (in vivo)

Mice: ALI induced by 30' mesenteric artery ischemia.

Simultaneously with reperfusion, IFN-beta iv (20.000 units).

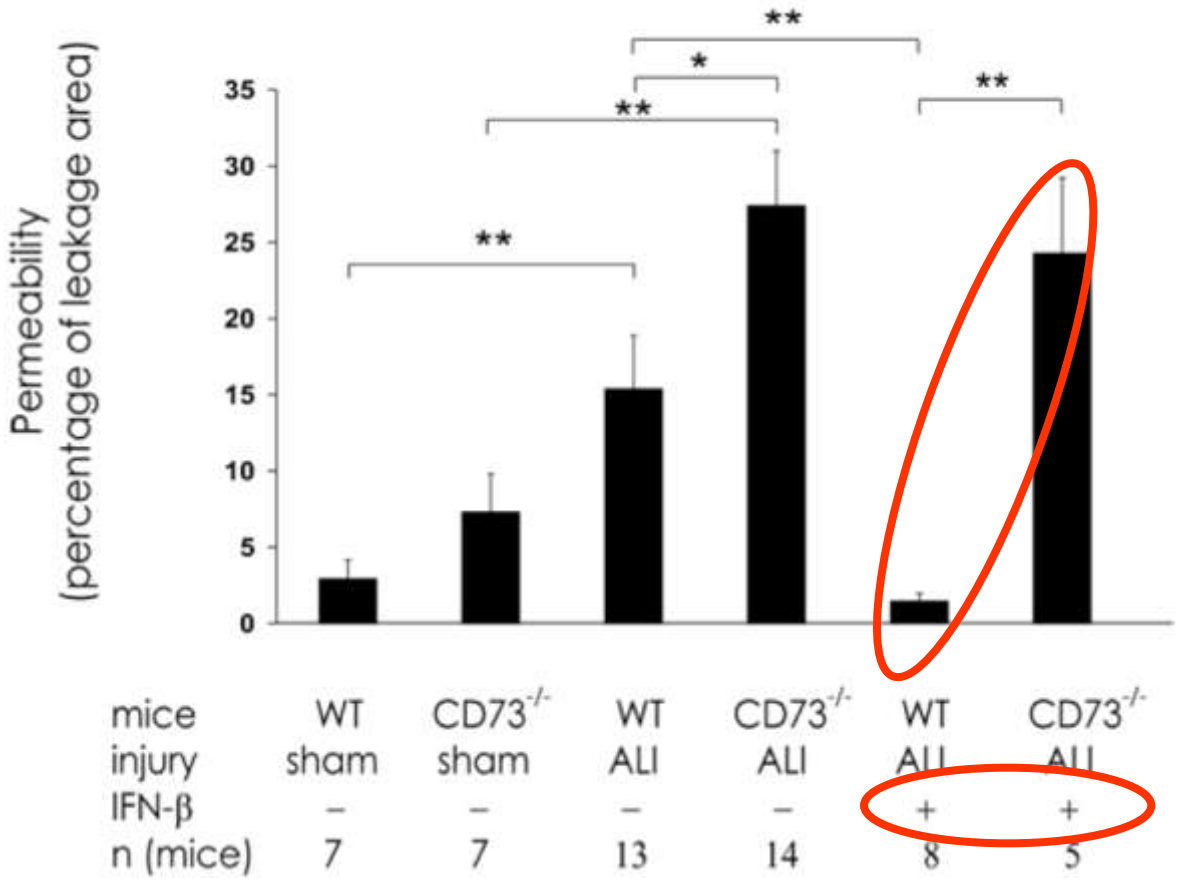
Five minutes prior euthanasia, FITC-dextran to measure lung leak.

(n=8-13±SEM).

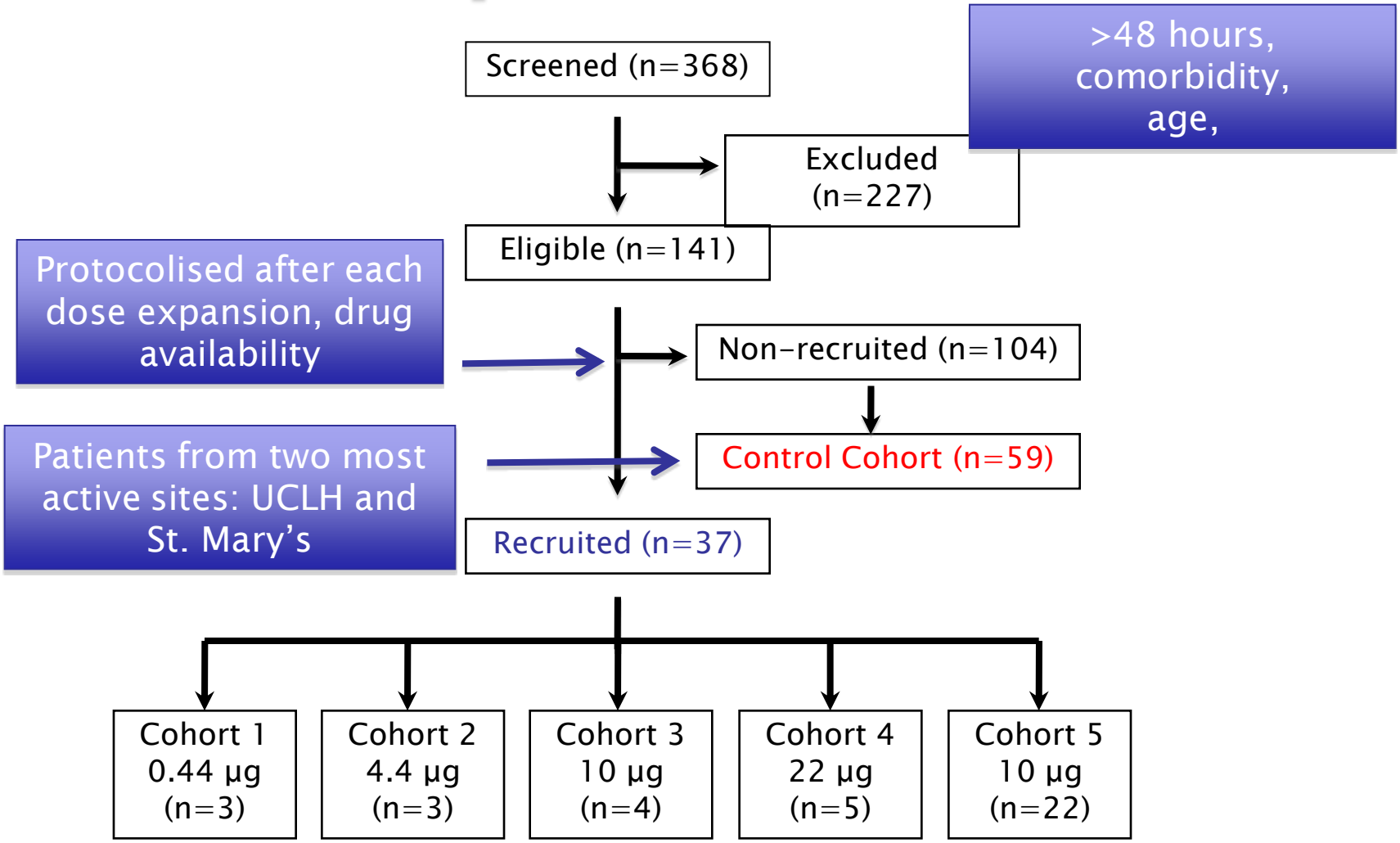


Kiss et al. (2007)
Eur. J. Immunol. 37:3334

IFN-beta prevention of lung leakage is CD73 dependent

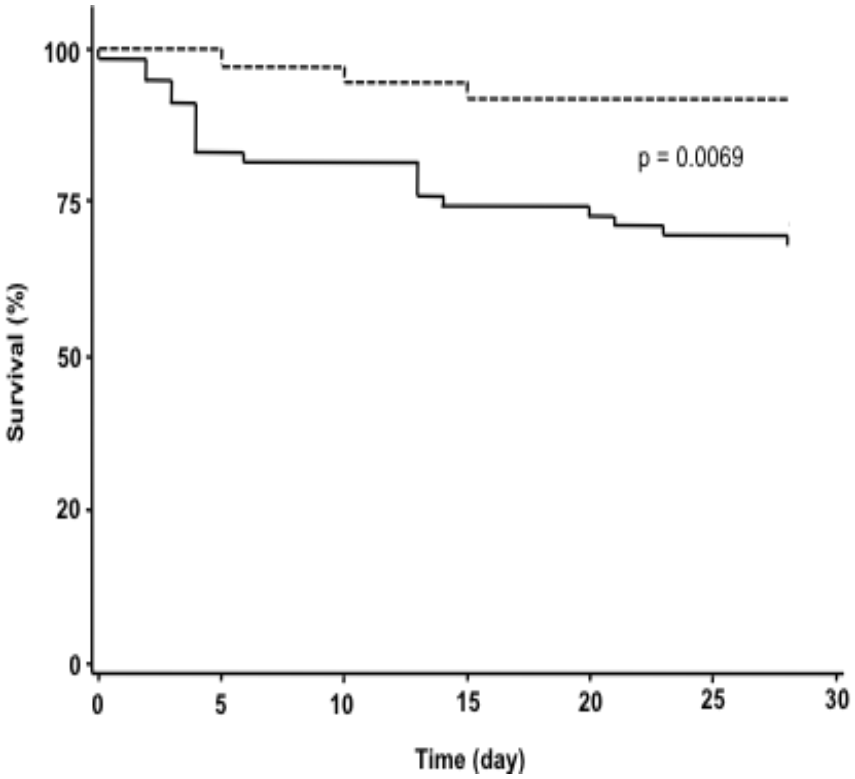


FPCLI001 patient recruitment



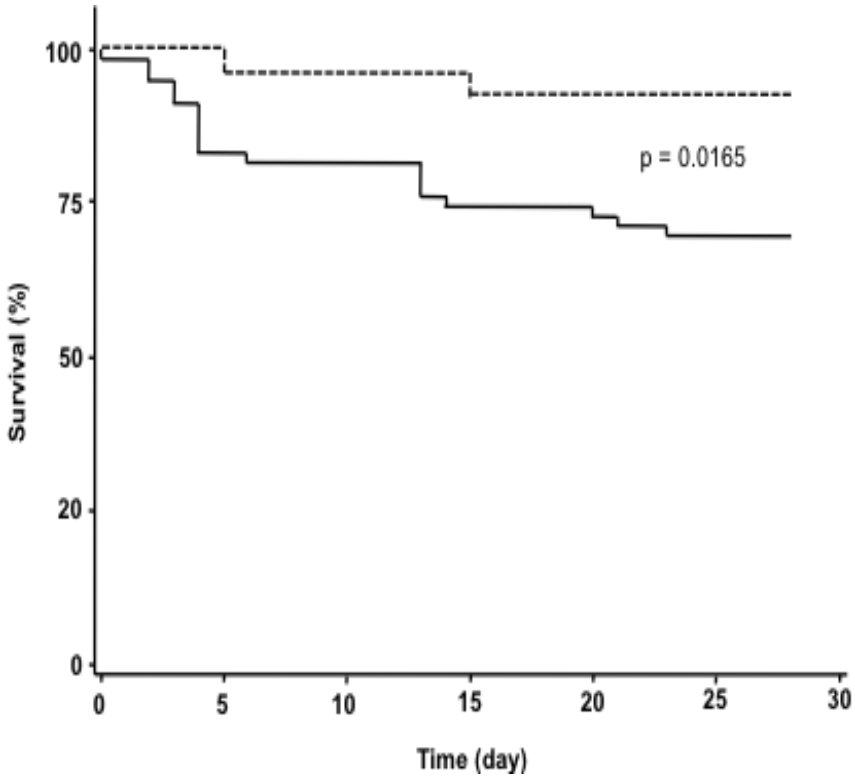
Survival

A



All 37 IFN-β treated patients

B



All 26 OTD IFN-β treated patients

Negative Trials

- NO
- Continuous rotation
- Prostaglandin Inhibitors (Ketoconazole, Ibuprofen)
- Antioxidants (N-acetyl cysteine, procysteine, free radical scavengers)
- Almitrine

Not sure

- ECMO
- Oscillation
- Continuous supraglottic aspiration?