Steroids in ARDS:
if, when, how much?

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Steroids in ARDS: conclusion

- Give low-dose steroids if indicated for another problem (hydrocortisone 200-300 mg/day for 7 d)
  - Septic shock (sepsis + fluids + vasopressors)
  - Eosinophilic pneumonia
  - *Pneumocystis* pneumonia
  - Adrenocortical insufficiency

- Steroids are *not* indicated for routine prophylaxis or treatment of ARDS

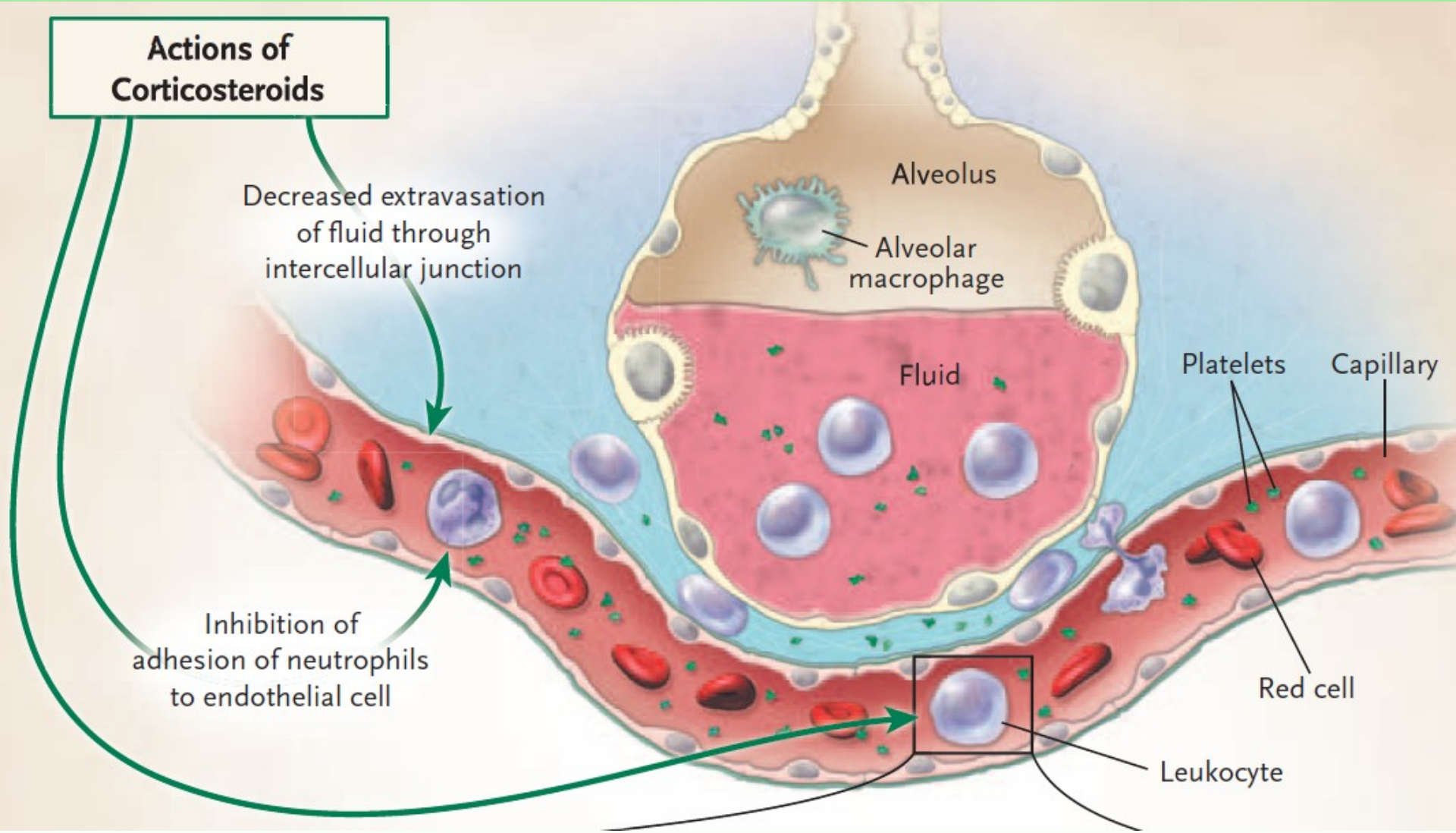
Why *might* steroids make sense?

- Pathophysiology of ARDS = ***neutrophil activation and endothelial injury*** after pulmonary insult:
  - **Pneumonia**, gastric aspiration, fat emboli, **inhalation injury**, fat emboli, lung contusion
- after extrapulmonary insult:
  - **Sepsis**, multiple trauma, CABG, pancreatitis, burns, drug overdose, blood transfusion
- Increased risk of ARDS with predisposing medical disorders, alcohol abuse, COPD, acidemia

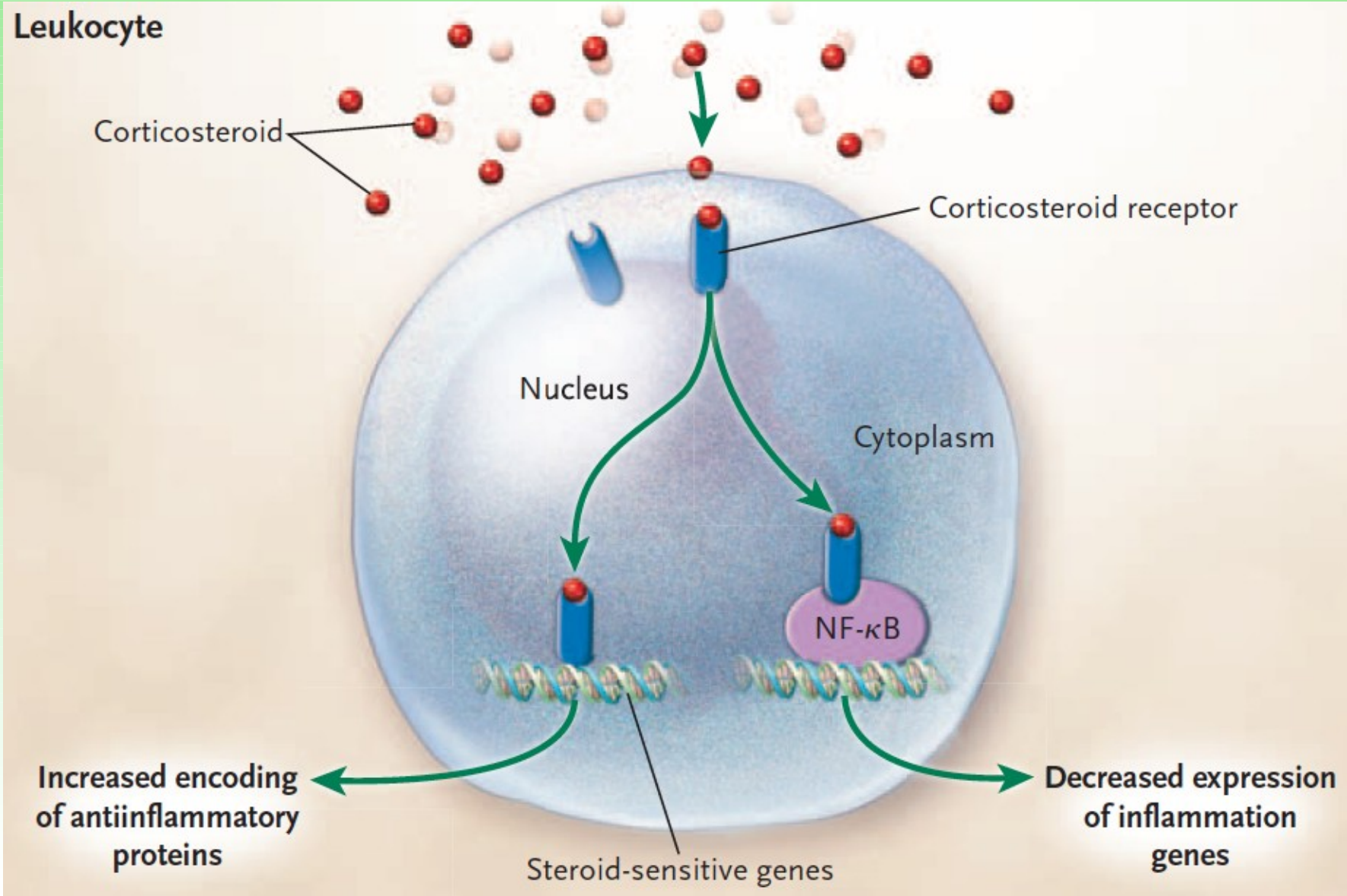
Why *might* steroids make sense?

- Pathophysiology of ARDS = ***neutrophil activation and endothelial injury*** after pulmonary and extrapulmonary insults
- = many, many inflammatory molecules…
  - Interleukin-6, -8, -10, -1ß
  - Tumor necrosis factor (TNF-α)
  - Interferon-γ

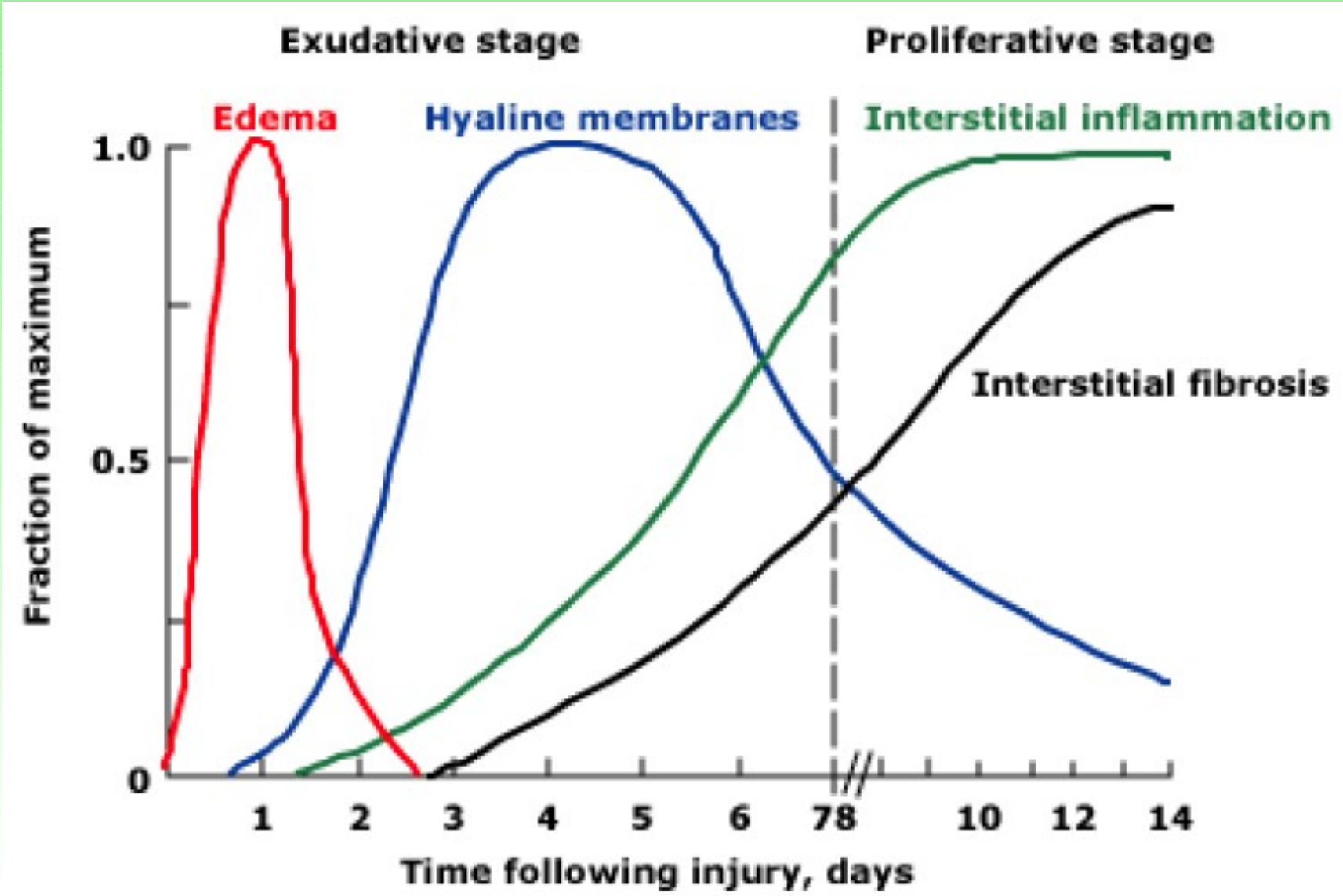
Extracellular effects of corticosteroids

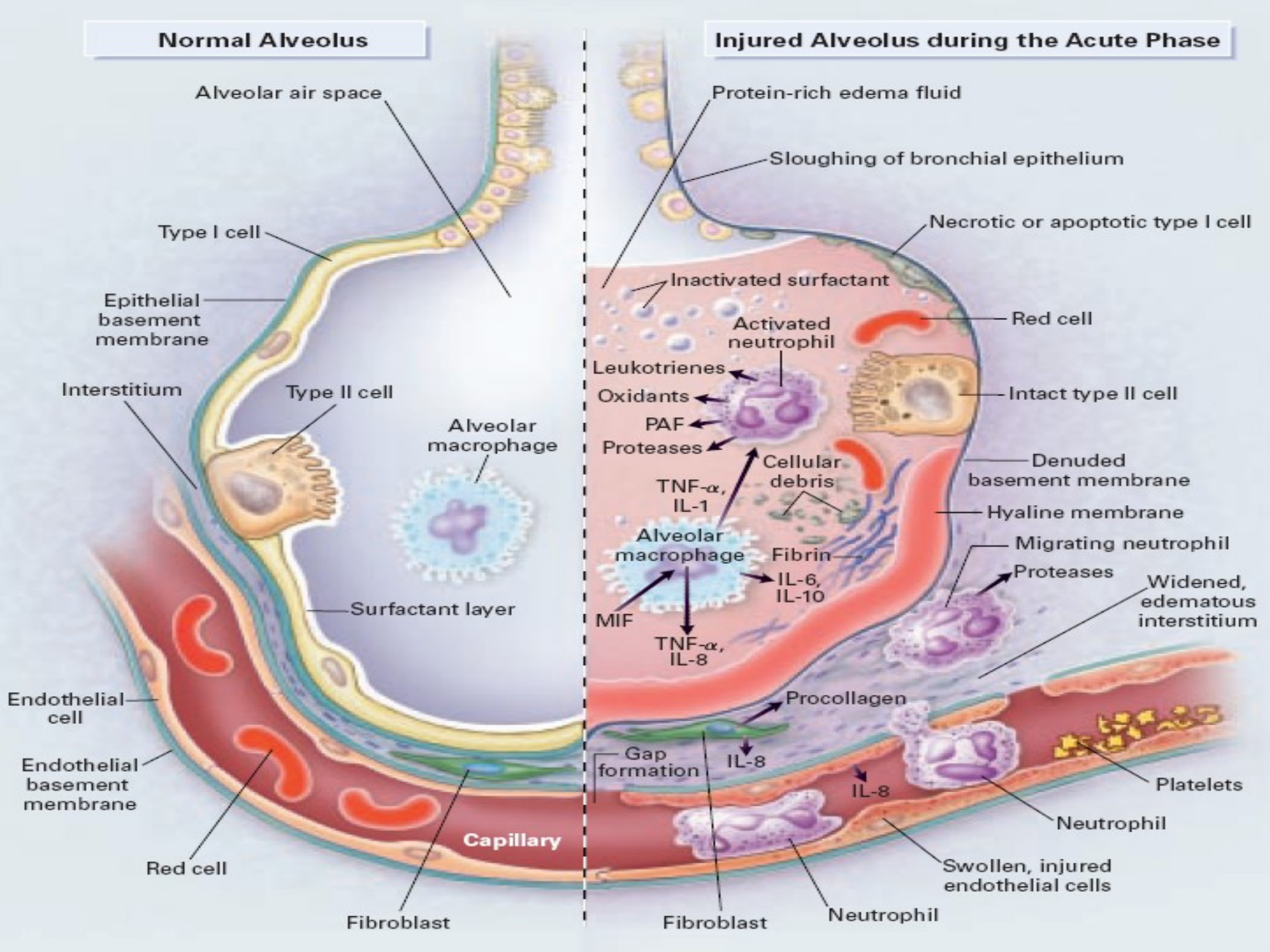


Intracellular effects of corticosteroids

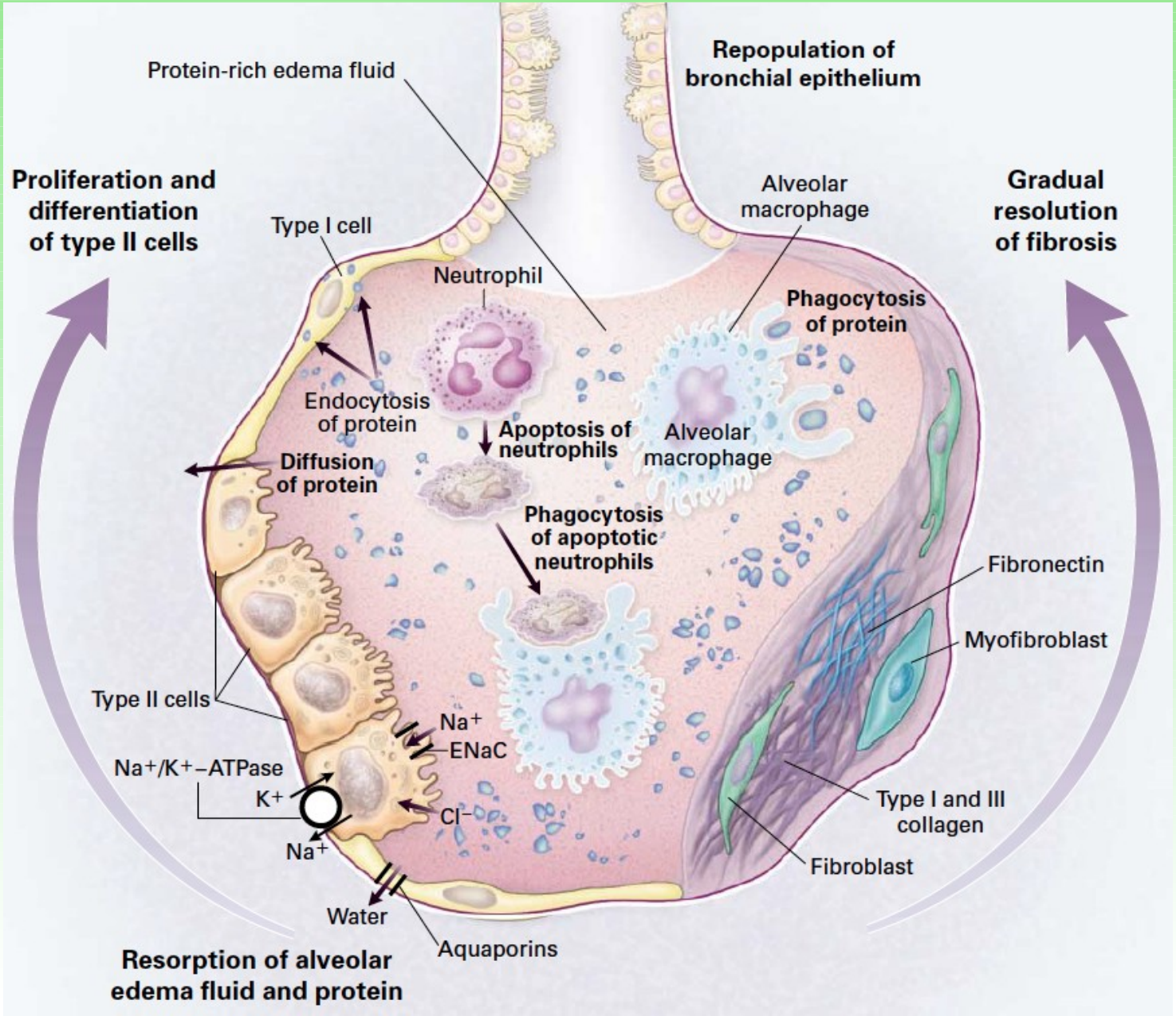


Time course of ARDS




Normal Alveolus
Injured Alveolus during the Acute Phase
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Red cell
Capillary
Fibroblast
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Red cell
Activated neutrophil
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNF-α, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
Proteases
IL-6, IL-10
MIF
TNF-α, IL-8
Widened, edematous interstitium
Procollagen
Gap formation
IL-8
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

Proliferative and fibrosis phases of ARDS



Definition of ARDS (Berlin, 2012)

- Within one week of insult
- Bilateral opacities not explained by effusions, lobar collapse, or nodules
- Respiratory failure not explained by cardiac failure or fluid overload (assess objectively to exclude hydrostatic edema; for example, with echocardiography)
- Oxygenation:
  - Mild: with PEEP or CPAP ≥5 cm H_2O, 200< PaO_2/FiO_2 ≤300
  - Moderate: with PEEP ≥5 cm H_2O, 100< PaO_2/FiO_2 ≤200
  - Severe: with PEEP ≥5 cm H_2O, PaO_2/FiO_2 ≤100

Steroids given for prevention of ARDS

- All studies done in the 1980's
- Steroids:
  - More patients developed ARDS
  - More patients died

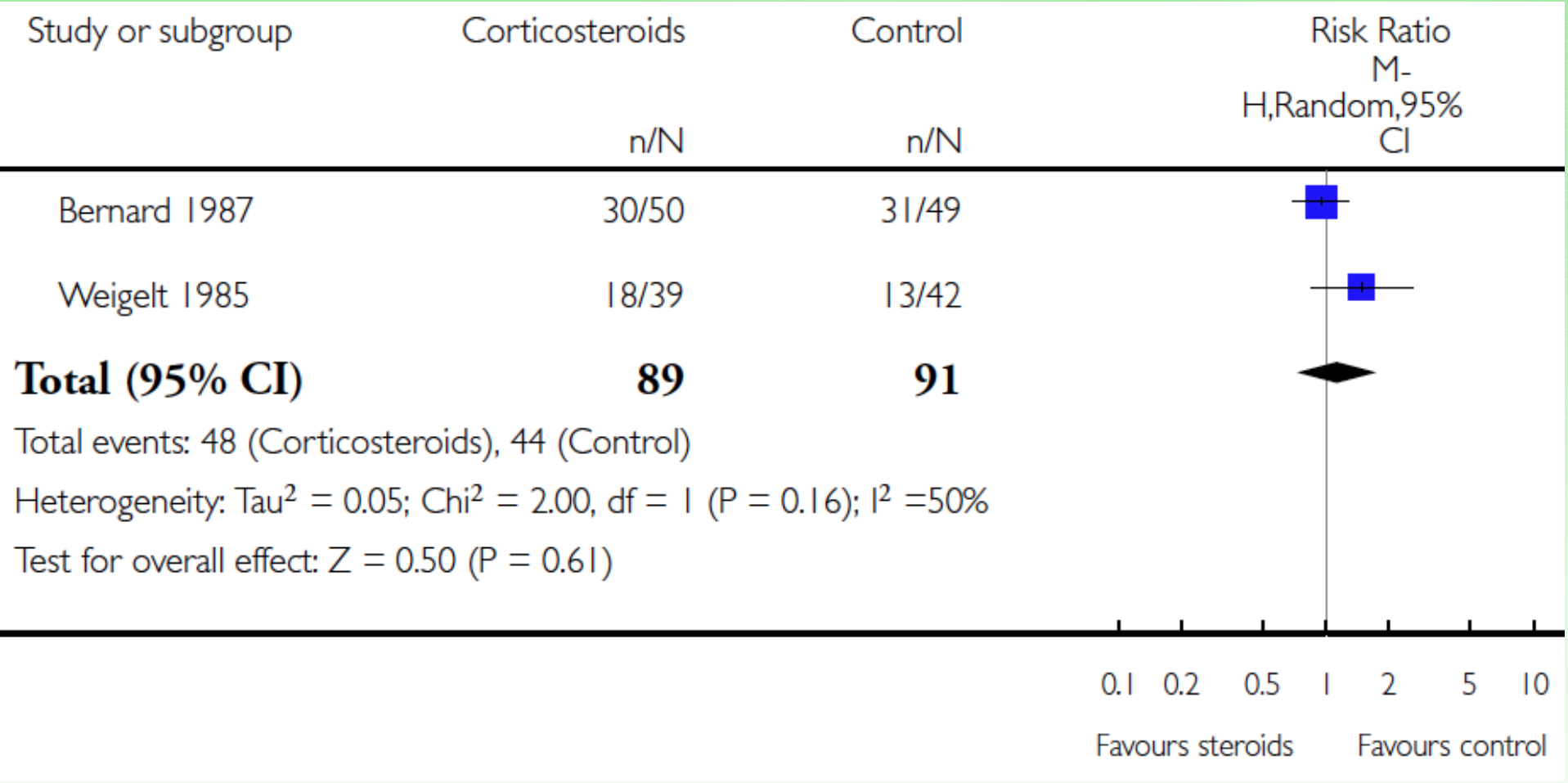
	ARDS Risk Factors (N.)	Odds Ratio developing ARDS	Odds Ratio to death if ARDS developed
1985	Septic shock (81)	2.36 (1.14-6.28)	1.23 (0.37-3.66)
1987	Severe sepsis (304)	1.48 (0.93-2.34)	2.96 (1.25-7.73)
1987	Septic shock (42)*	1.48 (0.48-4.44)	Not applicable
1988	Septic shock (75)	1.15 (0.44-2.33)	0.93 (0.17-3.54)
—	—	1.55 (0.58-4.05)	1.52 (0.30-5.94)

Randomized controlled trials using steroids in ARDS

- High-dose steroids given ***early*** for ARDS:
  - No benefit
  - Increased rate of infectious complications
  - *1985 Arch Surg. Early steroid therapy for respiratory failure.*
  - *1987 NEJM. High-dose corticosteroids in patients with the adult respiratory distress syndrome.*

Randomized controlled trials using steroids in ARDS

- High-dose steroids given ***early*** for ARDS:



Steroids given for the treatment of established ARDS

- Some studies had very few patients… results were very variable

	ARDS duration (N.)	Odds ratio for death
1987	Early (99)	0.75 (0.41-1.57)
1998	Late (24)*	0.41 (0.06-0.99)
2006	Late (180)	0.84 (0.49-1.60)
2006	Early (177)	0.66 (0.38-1.13)
2007	Early (91)*	0.53 (0.21-1.01)
—	—	0.62 (0.23-1.26)

Randomized controlled trials using steroids in ARDS

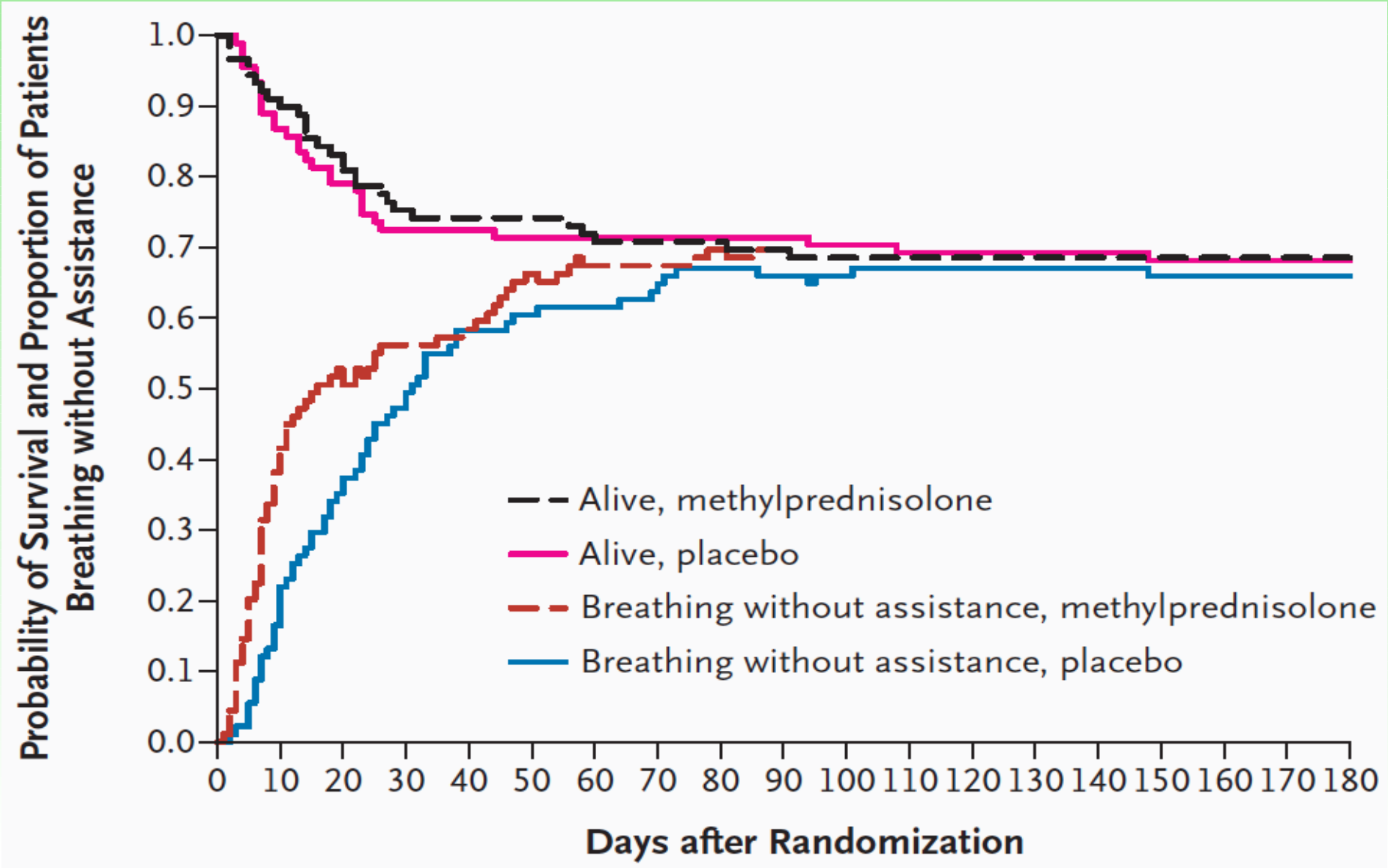
- Steroids given ***late*** in ARDS:
  - Survival benefit (24 patients)
  - No survival benefit (180 patients)
  - *1998 JAMA. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome.*
  - *2006 NEJM. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome.*

Randomized controlled trials using steroids in ARDS

- 2006 NEJM. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome
  - N=180, all with ARDS for at least 7 days
  - No difference in mortality at 60 days or at 180 days
  - Steroid group had better oxygenation, more ventilator-free days
  - Steroid group had more neuromyopathy, more hyperglycemia
  - If given after 14 days, steroids **increased** mortality

Randomized controlled trials using steroids in ARDS

- 2006 NEJM. Efficacy and safety of corticosteroids



Randomized controlled trials using steroids in ARDS

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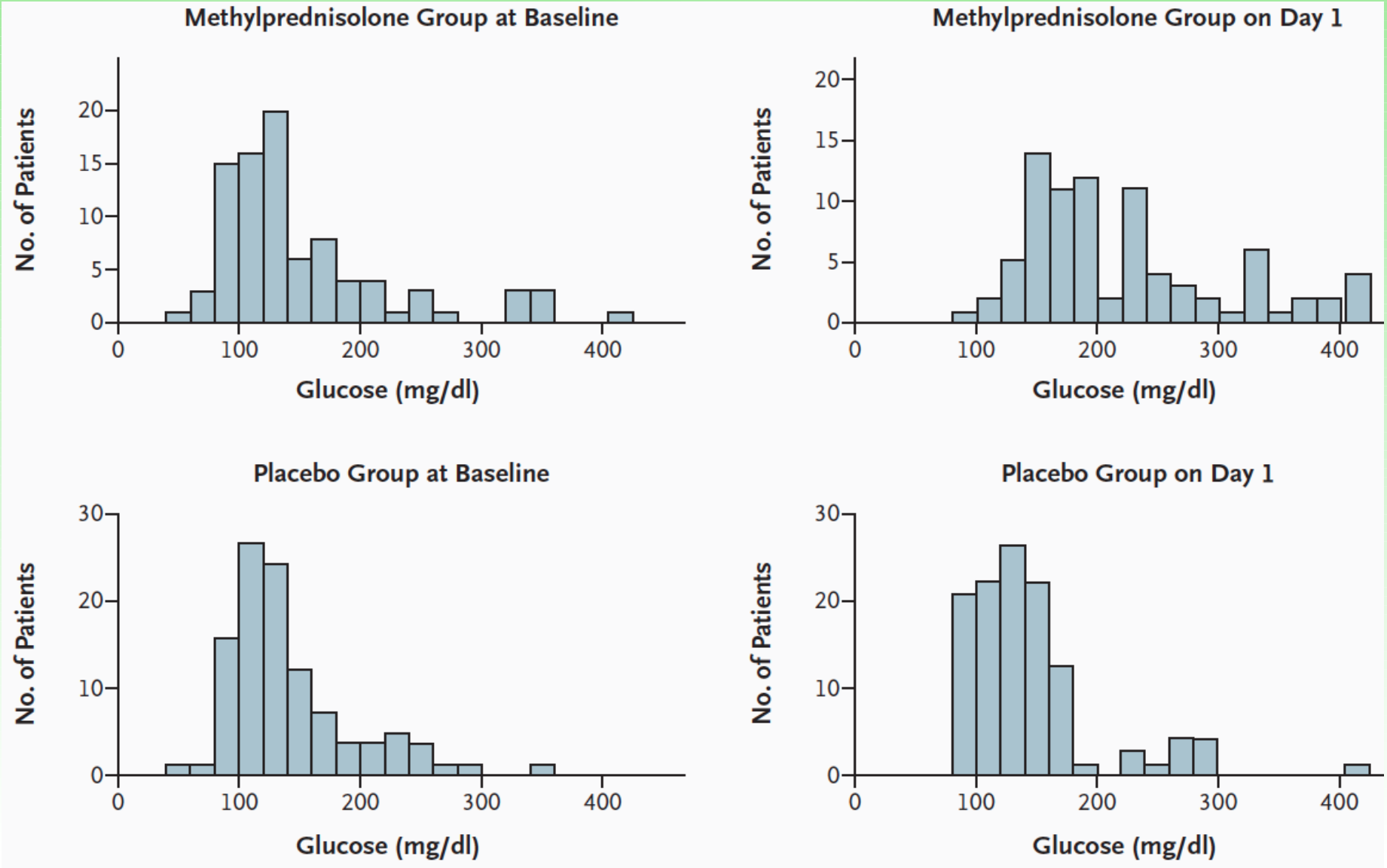

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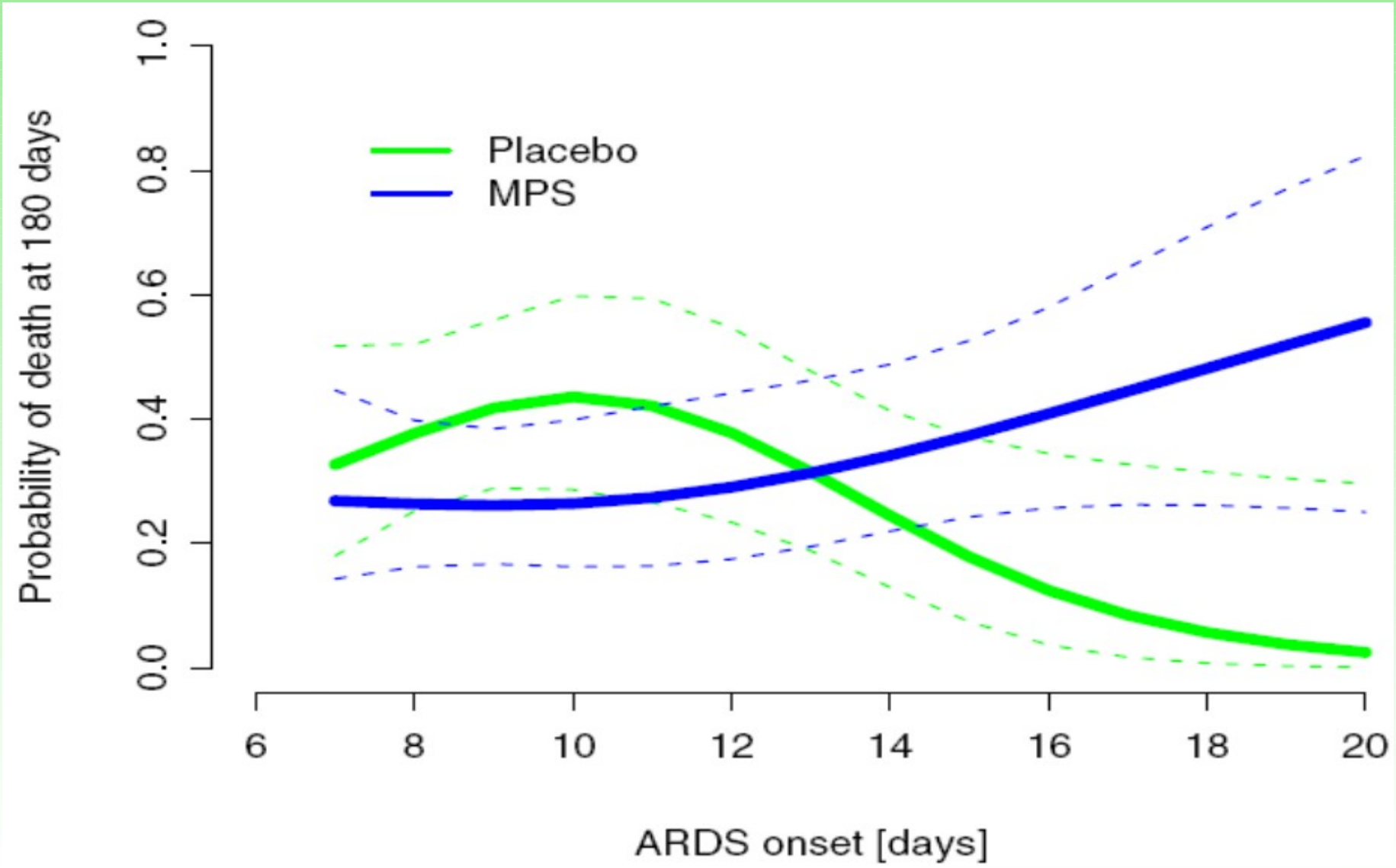
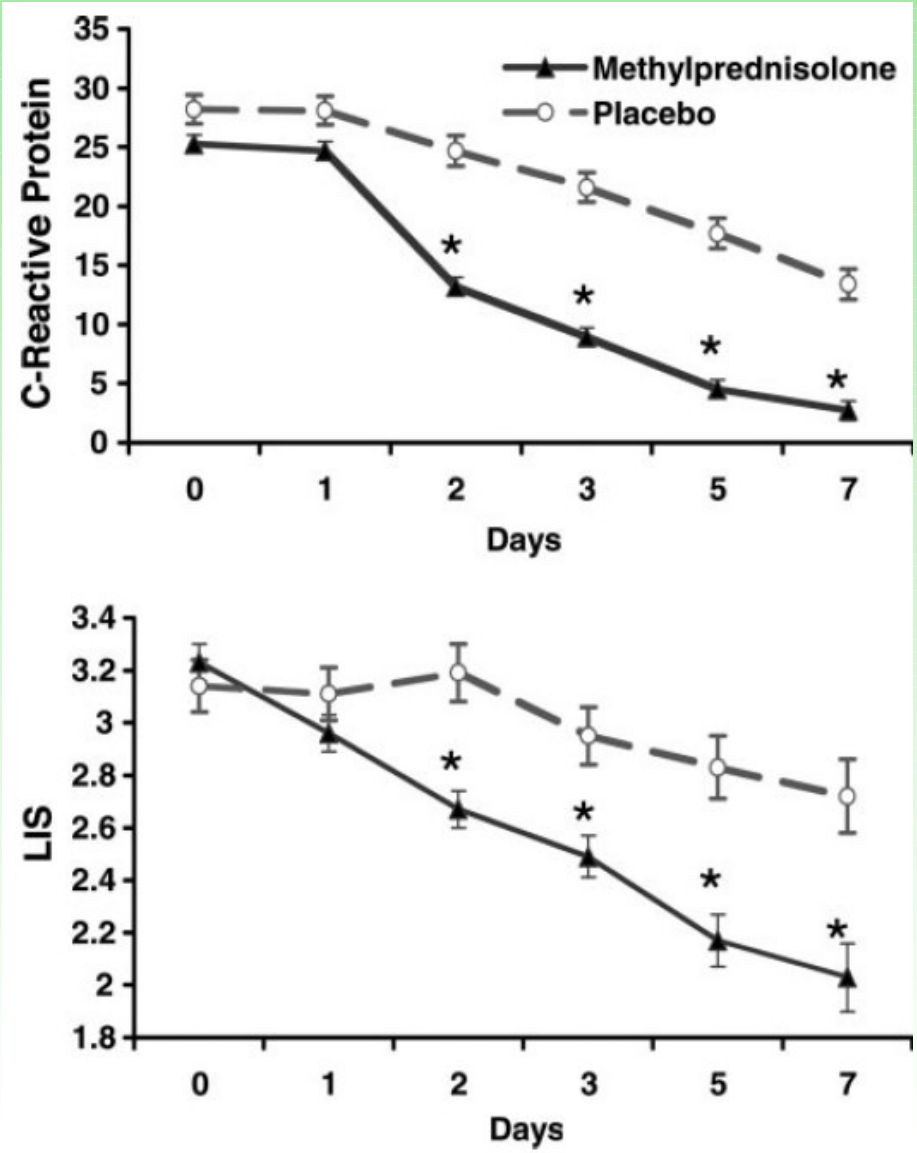


Randomized controlled trials using steroids in ARDS

- 2007 Methylprednisolone infusion in early severe ARDS
- N=91, sepsis in 66%, steroids started within 72 hrs
- Survival was not a primary outcome (!)
- Primary outcomes were decrease in lung injury score and C-reactive protein levels

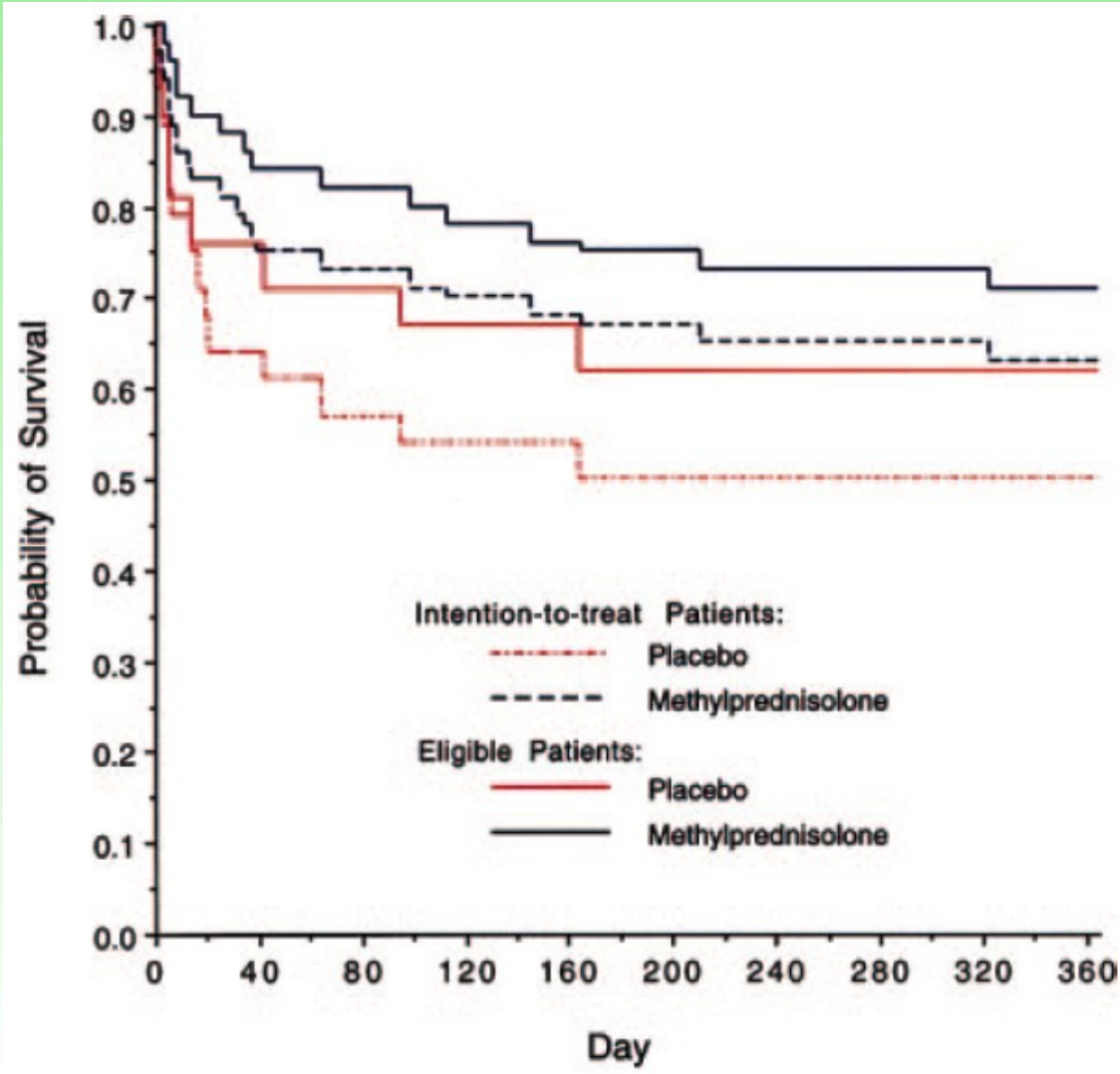
Randomized controlled trials using steroids in ARDS

- 2007 Methylprednisolone infusion in early severe ARDS



Randomized controlled trials using steroids in ARDS

- 2007 Methylprednisolone infusion in early severe ARDS
- At 28 days, the difference in survival was *not* significantly different. p=0.20



Randomized controlled trials using steroids in ARDS

- **2011 Early Corticosteroids in Severe Influenza A/H1N1 Pneumonia and ARDS**
- Retrospective study of 208 pts with ARDS and influenza A/H1N1
  - No steroids n=125 Steroids n=83
- Steroid group
  - More deaths (34% vs 17%)
  - More ICU-acquired infections (45% vs 35%)
  - More ICU-acquired pneumonia (41% vs 26%)

Randomized controlled trials using steroids in ARDS

- 2011, retrospective, multicenter, 245 patients
- 90-day mortality
  - 58% steroids
  - 27% no steroids
- Steroid group
  - more superinfections
  - longer ICU stay

Corticosteroid Treatment in Critically Ill Patients with Pandemic Influenza A/H1N1 2009 Infection

Analytic Strategy Using Propensity Scores

ARDS caused by inhalational injury

- Only 13 studies (mostly animal) found for a meta-analysis
- No benefit in the acute phase
- Harm if given in the late phase

- No data exists for corticosteroid treatment of patients with inhalational exposures

ARDS caused by aspiration of gastric contents

- One randomized trial
  - no difference in outcomes

- Case-control study
  - No difference in mortality
  - Ventilator days fewer in steroid group
  - More gram-negative pneumonia in steroid group

= steroids are not recommended in these patients

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2013: an interesting question:

Current Opinion in Anaesthesiology:
April 2013 - Volume 26 - Issue 2 - p 164–170
doi: 10.1097/ACO.0b013e32835e820e
ETHICS, ECONOMICS AND OUTCOME: Edited by David M. Rothenberg

Do corticosteroids improve outcome for any critical illness?

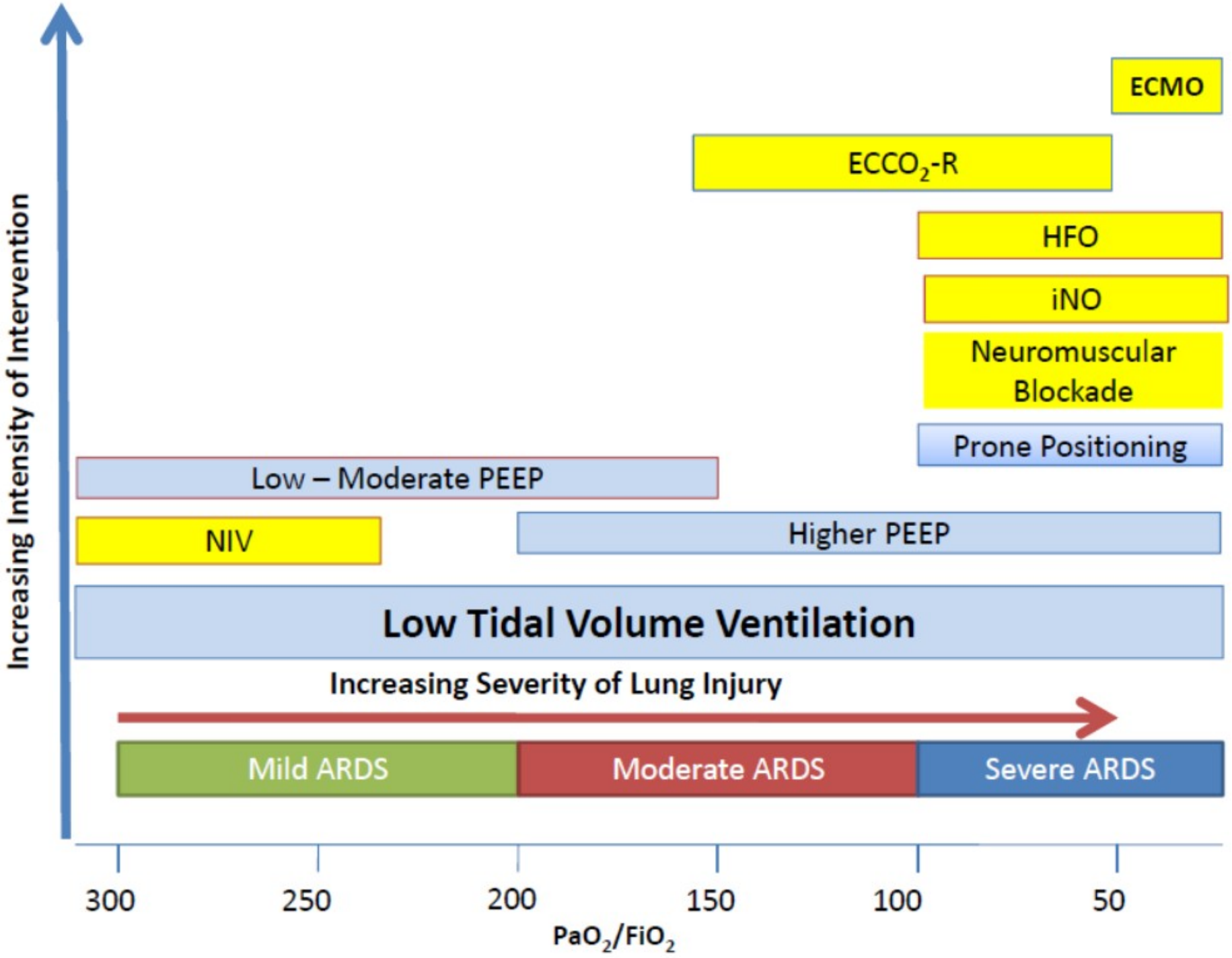
Batzofin, Baruch M.; Weiss, Yoram G.; Ledot, Stephane F.

If you decide to give steroids…

- Do not give etomidate
- Do not give neuromuscular blockers
- Taper the steroids s-l-o-w-l-y…

If not steroids, what can we do for ARDS pts?

- FiO_2 <0.6
- **Tidal volume 6 mL/kg (predicted body weight)**
- Plateau pressures <30 cm H_2O
- Recruitment maneuvers / PEEP (individualized)
- **Fluid restriction, restricted transfusion protocols**
- [Prone positioning, inhaled nitric oxide, neuromuscular blockers]
- [High-freq. oscillatory ventilation, ECMO]


ECMO
ECCO2-R
HFO
iNO
Neuromuscular Blockade
Prone Positioning
Low – Moderate PEEP
NIV
Higher PEEP
Low Tidal Volume Ventilation
Increasing Intensity of Intervention
Increasing Severity of Lung Injury
Mild ARDS
Moderate ARDS
Severe ARDS
300
250
200
150
100
50
PaO2/FiO2

An ideal study design for steroids in ARDS:

- Who: worsening or unresolving ARDS, despite receiving optimal supportive therapy
  - Abx, source control of infxn, lung-protective ventilation, fluid restriction, restrictive blood transfusion protocols
- When: during the first week
- Design: randomized, double-blind, placebo-controlled
- Stratify randomization according to shock and vasopressor use
- Endpoints: mortality, ICU length of stay, **long-term functional outcomes**, adverse events

Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis*

Benjamin M. P. Tang, PhD; Jonathan C. Craig, PhD; Guy D. Eslick, PhD; Ian Seppelt, MBBS; Anthony S. McLean, MBBS

Conclusion: **The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions. The consistency of results in both study designs and all outcomes suggests that they are an effective treatment for ALI or ARDS. The mortality benefits in early ARDS should be confirmed by an adequately powered randomized trial.**

Crit Care Med 2009; 37:1594 –1603

2011: Even Dr. Meduri admits…

The balance of the available data… has a moderate degree of heterogeneity and provides weak evidence (grade 2B) for a survival benefit. Treatment decisions involve a tradeoff between benefits and risk, as well as costs.

Recent – ongoing studies related to ARDS

- Dexamethasone, cisatracurium, statins, omega-3 fatty acids, lipid emulsions, corticotropin injection, anticoagulants, aspirin, pentoxifylline, stem cells
- *Intrapleural* steroids
- ECMO
- PEEP / fluids / prone positioning / high-freq. oscillating vent., IL-6 removal by hemoperfusion

Recent – ongoing studies related to ARDS

- ~~Bevacizumab~~, dexamethasone, cisatracurium, statins, omega-3 fatty acids, lipid emulsions, corticotropin injection
- *Intrapleural* steroids
- ECMO
- PEEP / fluids / prone positioning / high-freq. oscillating vent., IL-6 removal by hemoperfusion
- Biomarkers (*many*), electrical impedance tomography monitoring

Questions? Comments?

http://www.ardsnet.org

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