Steroid Therapy in ARDS

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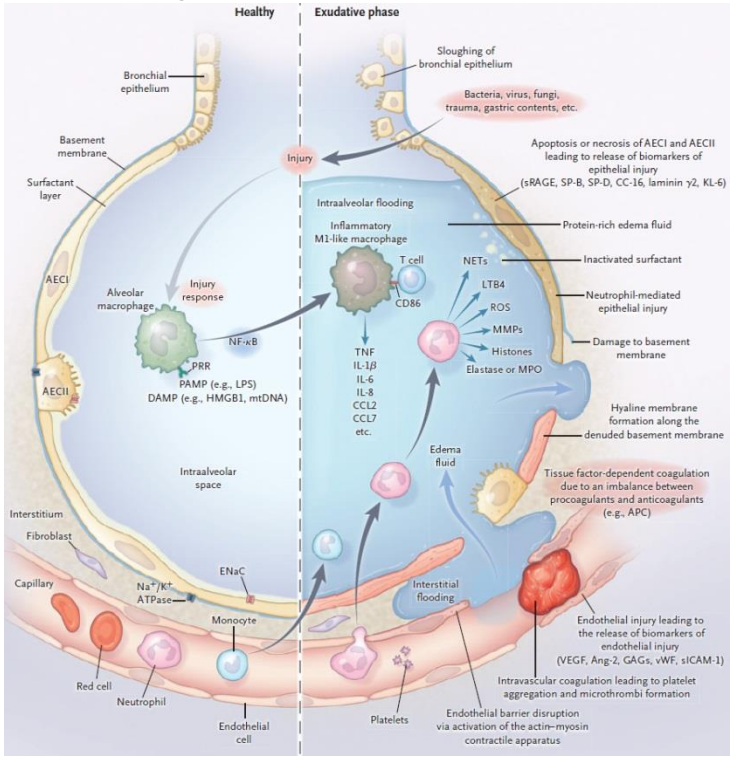
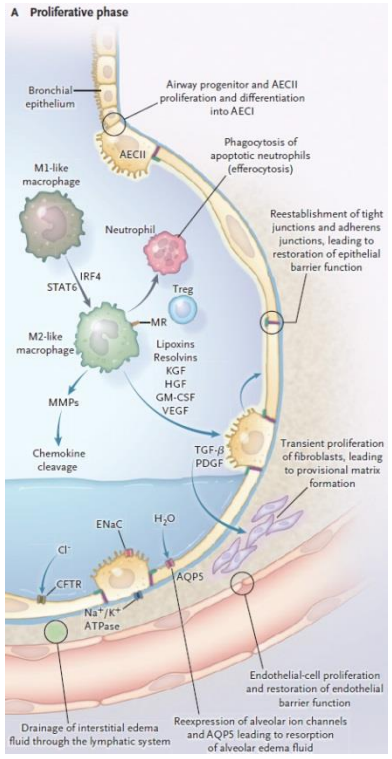
Clinical Course of ARDS

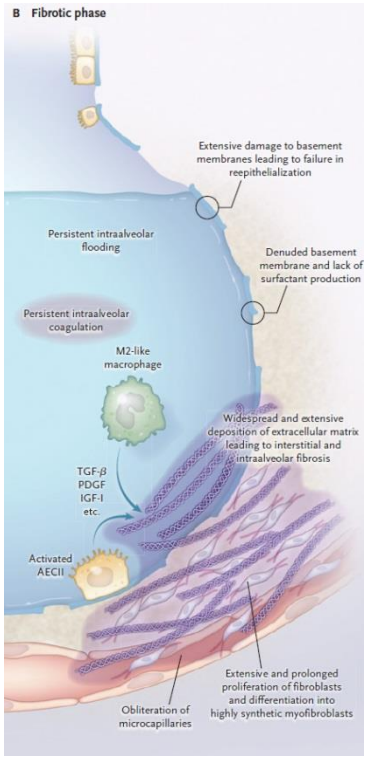
Exudative phase **Proliferative phase** **Fibrotic phase**

Edema Hyaline Membranes Interstitial Inflammation Fibrosis

Day: 0 2 7 14 21 . .



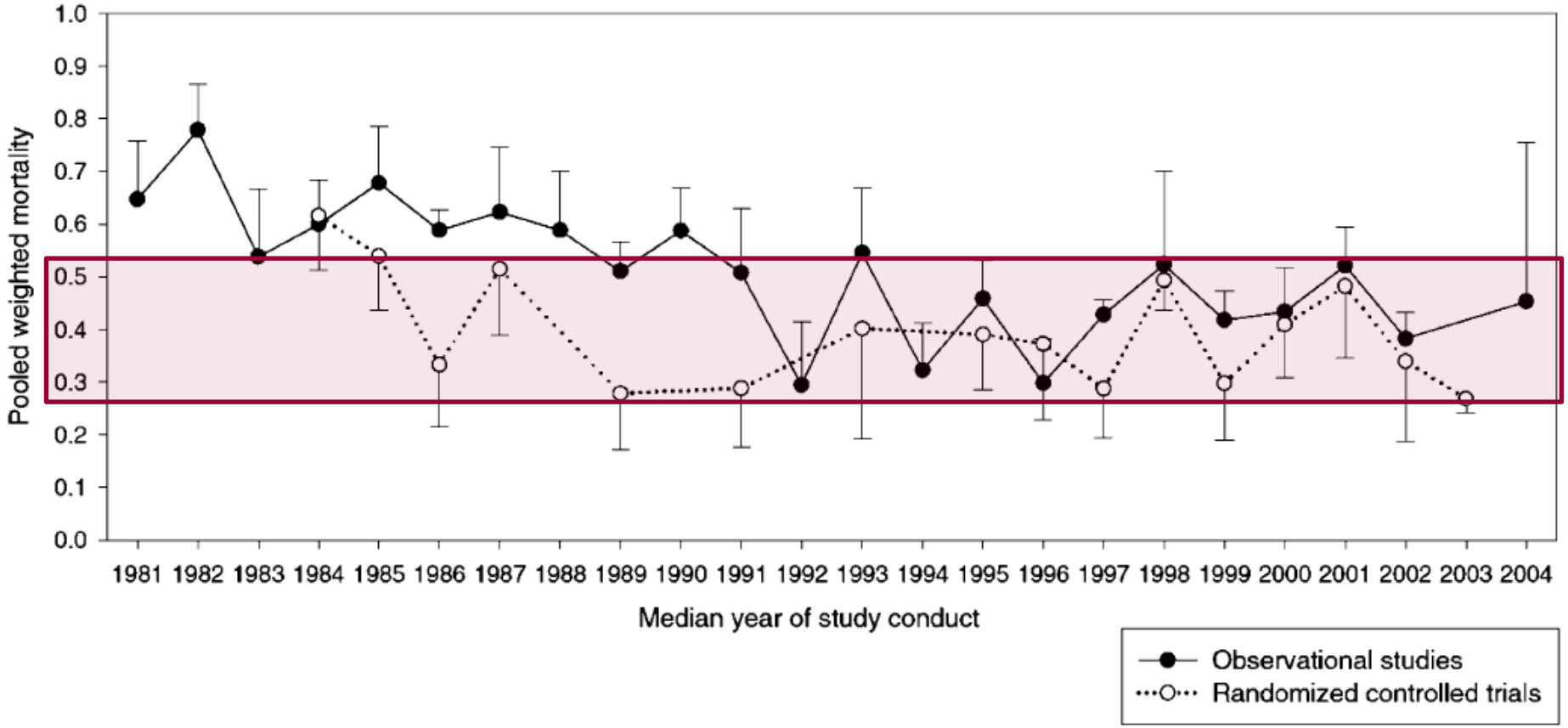




N Engl J Med 2017;377:562

Prognosis of ARDS

No Change of High Mortality Over Time



Am J Respir Crit Care Med 2009;179:220

Treatment of ARDS

No Specific Treatment

- General supportive care: mainstay of treatment
  - Recognition and treatment of the underlying medical and surgical disorders (e.g., sepsis, aspiration, trauma)
  - Minimizing procedures and their complications: lung protective ventilation
  - Prophylaxis against DVT, GI bleeding, aspiration, excessive sedation, and central venous catheter infections
  - Prompt recognition of nosocomial infections
  - Provision of adequate nutrition
- Fluid management: restrictive fluid balance
  - Increased ventilator free days, ICU free days

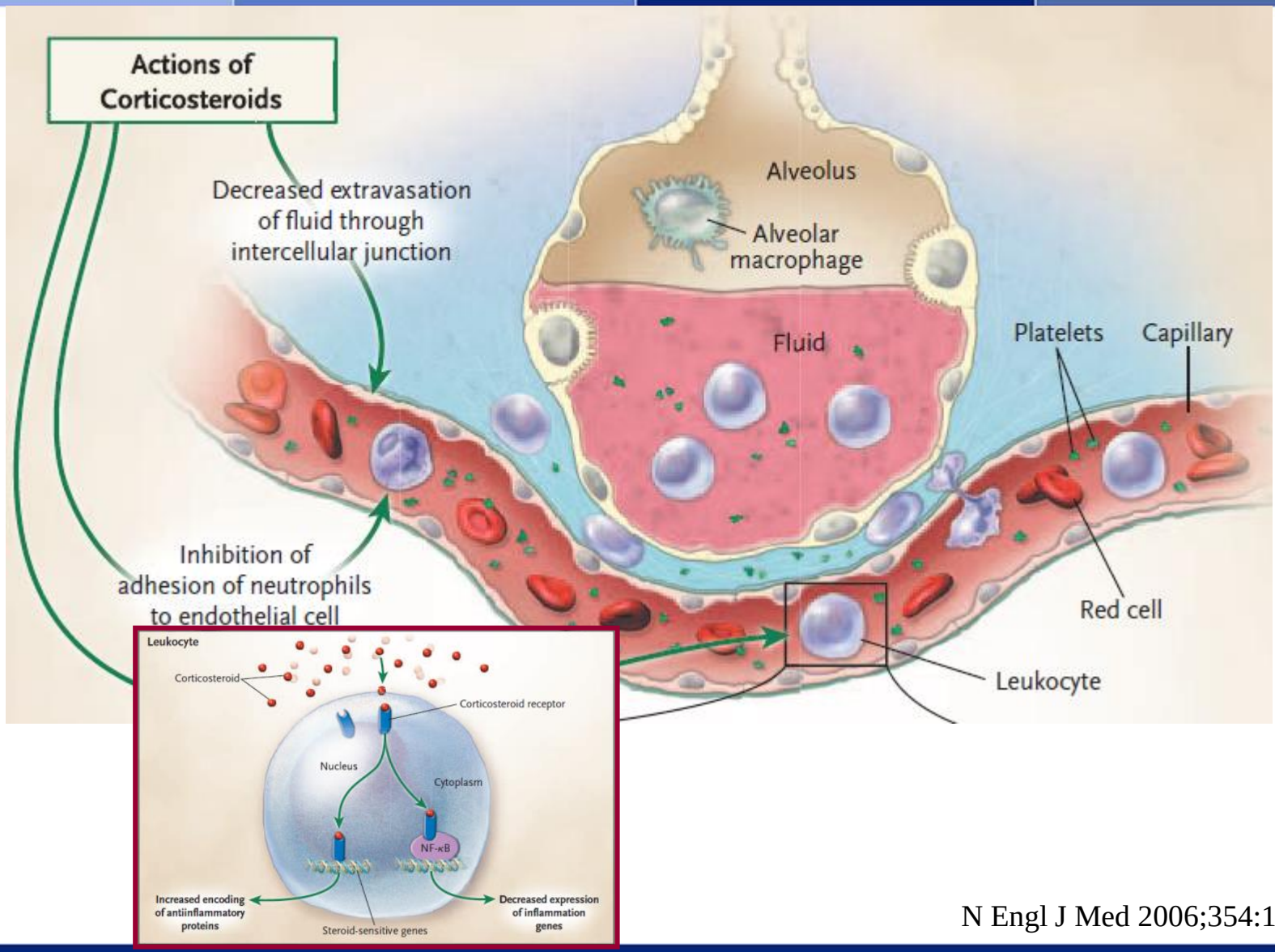
N Engl J Med 2006;354:2564-75

JAMA 2018;319:698

Pharmacotherapy for ARDS

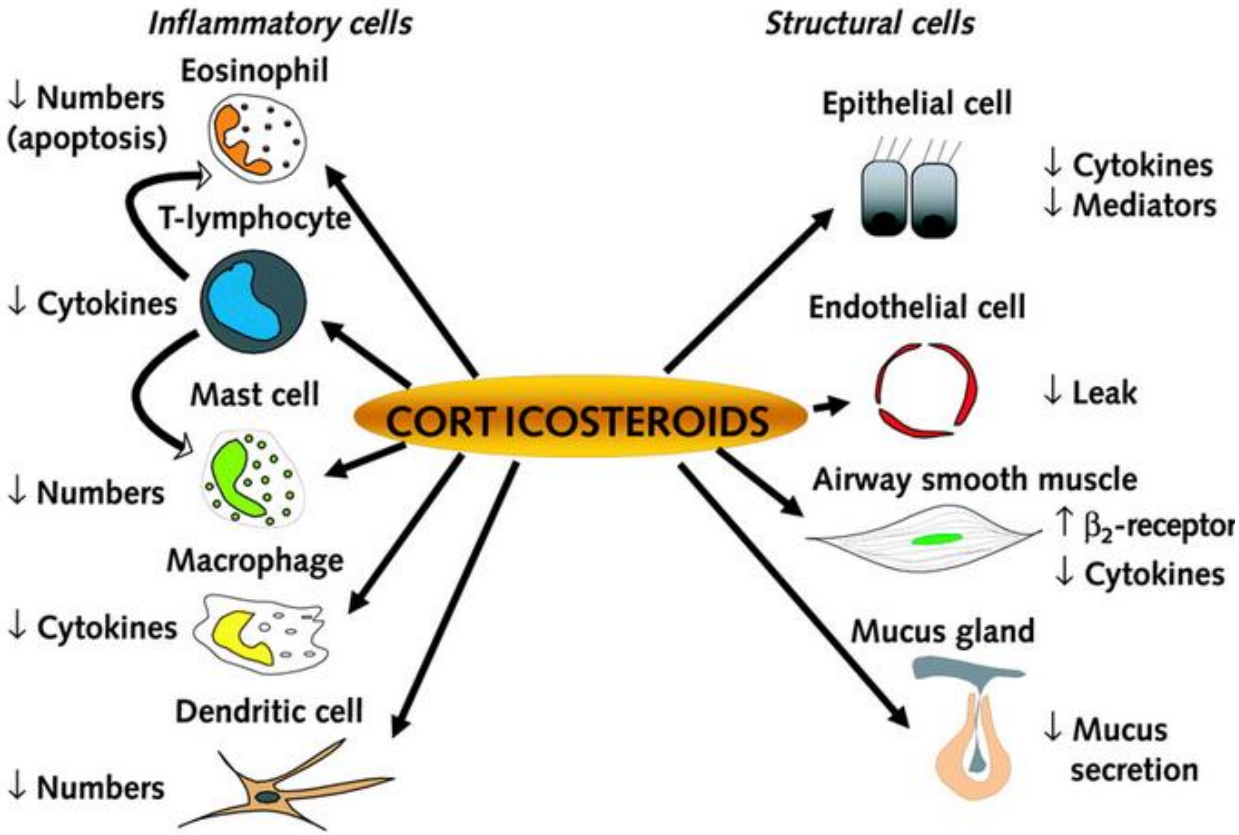
Proposed therapy	Impact on outcome	Major study
Surfactant	No effect	N Engl J Med 1996;334:1417
Liposomal prostaglandin E1	No effect	Crit Care Med 1999;27:1478
Ketoconazole	No effect	JAMA 2000;283:1995
Activated protein C	No effect	N Engl J Med 2001;344:699
Lisofylline	No effect	Crit Care Med 2002;30:1
Neutrophil elastase inhibitor	No effect	Crit Care Med 2004;32:169
Inhaled NO	No effect	JAMA 2004;291:1603
Omega-3 fatty acids	No effect	JAMA 2011;306:1574
Beta-adrenergic agonist	No effect	Lancet 2012;379:229
Corticosteroids	Mixed results	Controversial

Target for Corticosteroid Treatment
Inhibition of Inflammation



N Engl J Med 2006;354:1739

Corticosteroid for Preventing ARDS

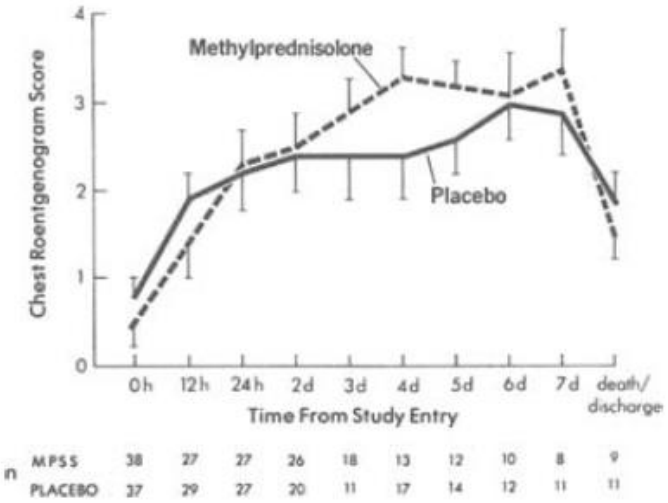


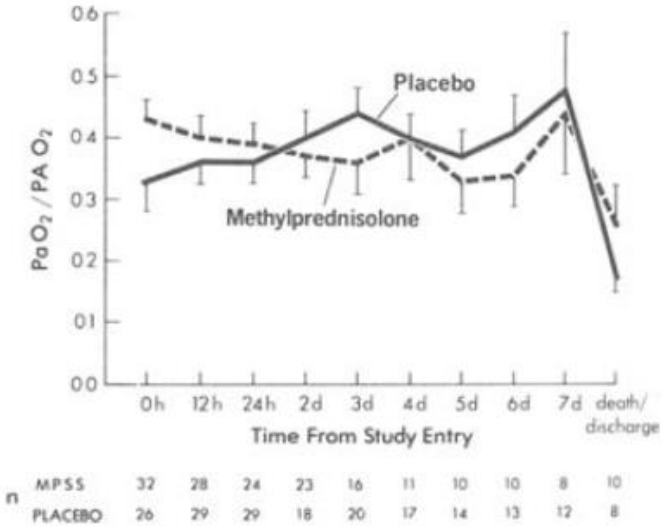
- Anti-inflammatory effect of corticosteroid might prevent or ameliorate parenchymal lung injury in patients with sepsis or risk for ARDS

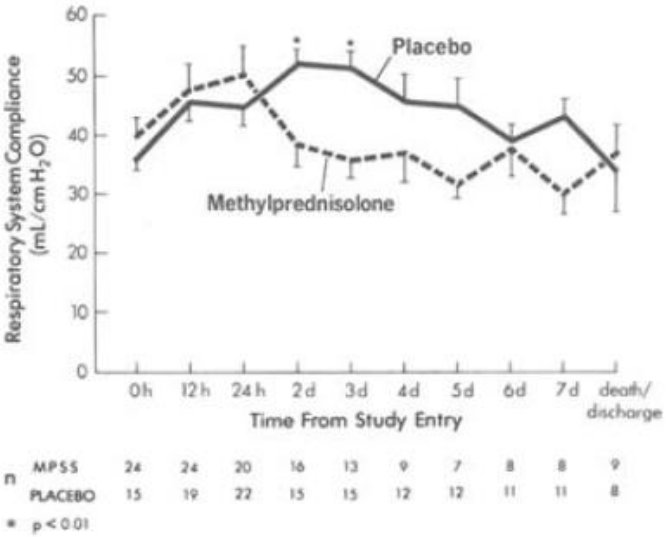
N EngI J Med 1981;305:456

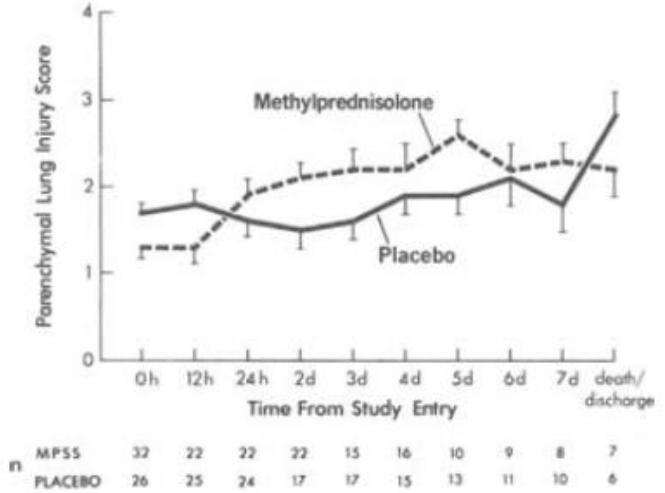
Corticosteroid for Preventing ARDS

30mg/kg every 6 h for 1 day









Am Rev Respir Dis 1988;138:62

Corticosteroid for Preventing ARDS

Summary of Trials

Study	Design	Underlying condition	Incidence of ARDS		
			Steroid group	Control group	*P* value
Sprung et al	RCT	Septic shock	24% (14% in DEXA)	13%	NA
Weigelt et al	RCT	Respiratory failure at risk for ARDS	64%	33%	0.008
Bone at al	RCT	Sepsis	32%	25%	0.1
Luce et al	RCT	Septic shock	34%	38%	NS

- No effect of early, short-course, high-dose corticosteroid on preventing the progression of ARDS

N Engl J Med 1984;311:1137
Arch Surg 1985;120:536
Chest 1987;92:1032
Am Rev Respir Dis 1988;138:62

High-dose Steroid Therapy in ARDS

Early, Short-course, High-dose

HIGH-DOSE CORTICOSTEROIDS IN PATIENTS WITH THE ADULT RESPIRATORY DISTRESS SYNDROME

GORDON R. BERNARD, M.D., JOHN M. LUCE, M.D., CHARLES L. SPRUNG, M.D., JEAN E. RINALDO, M.D., ROBERT M. TATE, M.D., WILLIAM J. SIBBALD, M.D., KHALIL KARIMAN, M.D., STANLEY HIGGINS, PH.D., ROBERTA BRADLEY, M.S.N., CRAIG A. METZ, M.S., THOMAS R. HARRIS, M.D., PH.D., AND KENNETH L. BRIGHAM, M.D.

Abstract Corticosteroids are widely used as therapy for the adult respiratory distress syndrome (ARDS) without proof of efficacy. We conducted a prospective, random-
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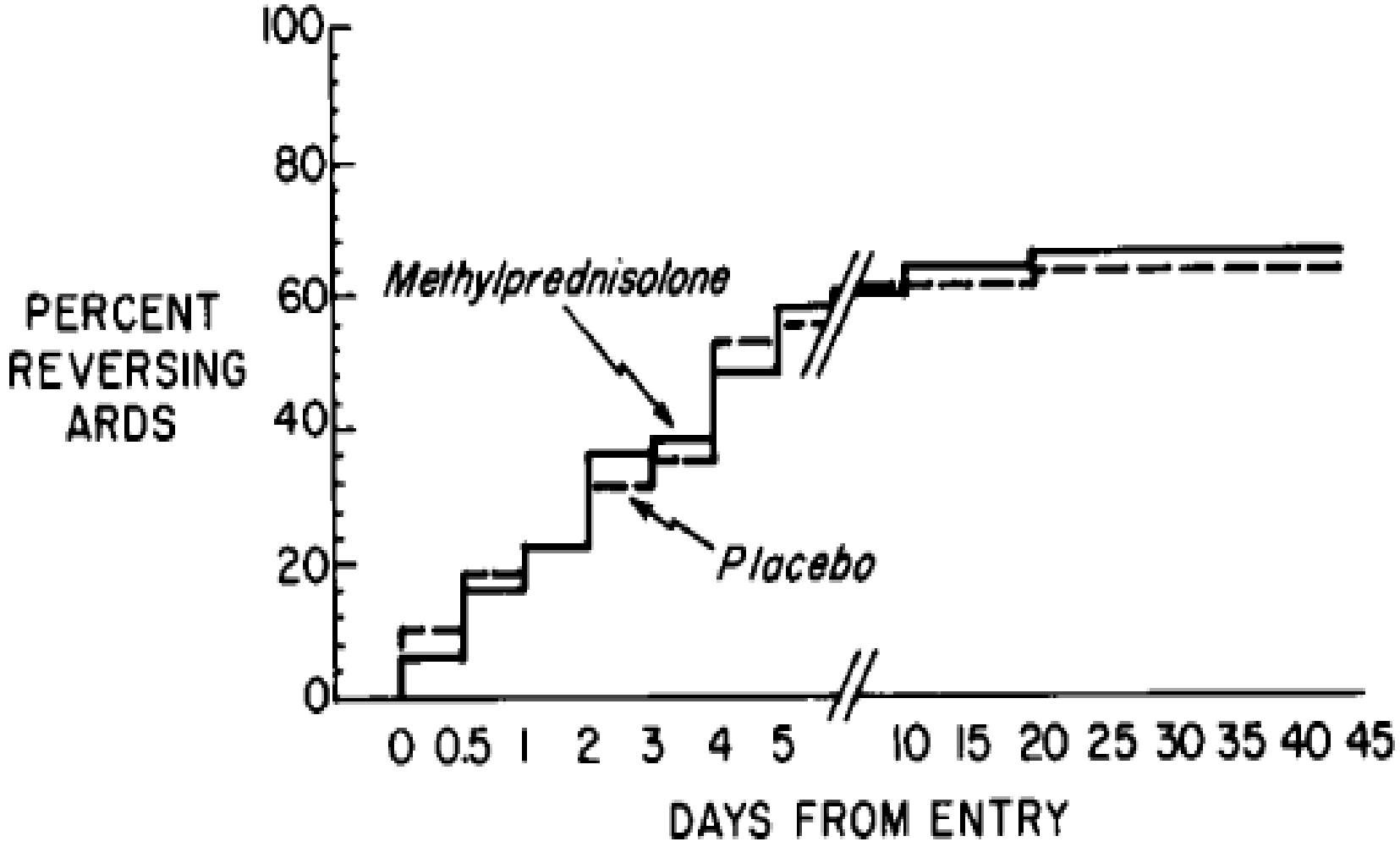
pressure of arterial oxygen to partial pressure of alveolar oxygen, the chest radiograph severity score, total thoracic compliance, and pulmonary-artery pressure.

We observed no statistical differences between groups in these characteristics upon entry or during the five days after entry. Forty-five days after entry there were
dnisolone and
30 of 50 [60
46 to 74] and
dence interval,
of ARDS (18
nt]; P = 0.77).
ntervals in the
clude a small
cations were
(8 of 50 [16
) [10 percent];
ablished ARDS
due to sepsis, aspiration, or a mixed cause, high-dose methylprednisolone does not affect outcome. (N Engl J Med 1987; 317:1565-70.)

	METHYL-PREDNISOLONE	PLACEBO
No. of patients	50	49
	mean ±SEM	
Age (yr)	55±2	56±2
Mechanical ventilation before entry (days)	2.8±0.5	1.9±0.4

High-dose Steroid Therapy in ARDS

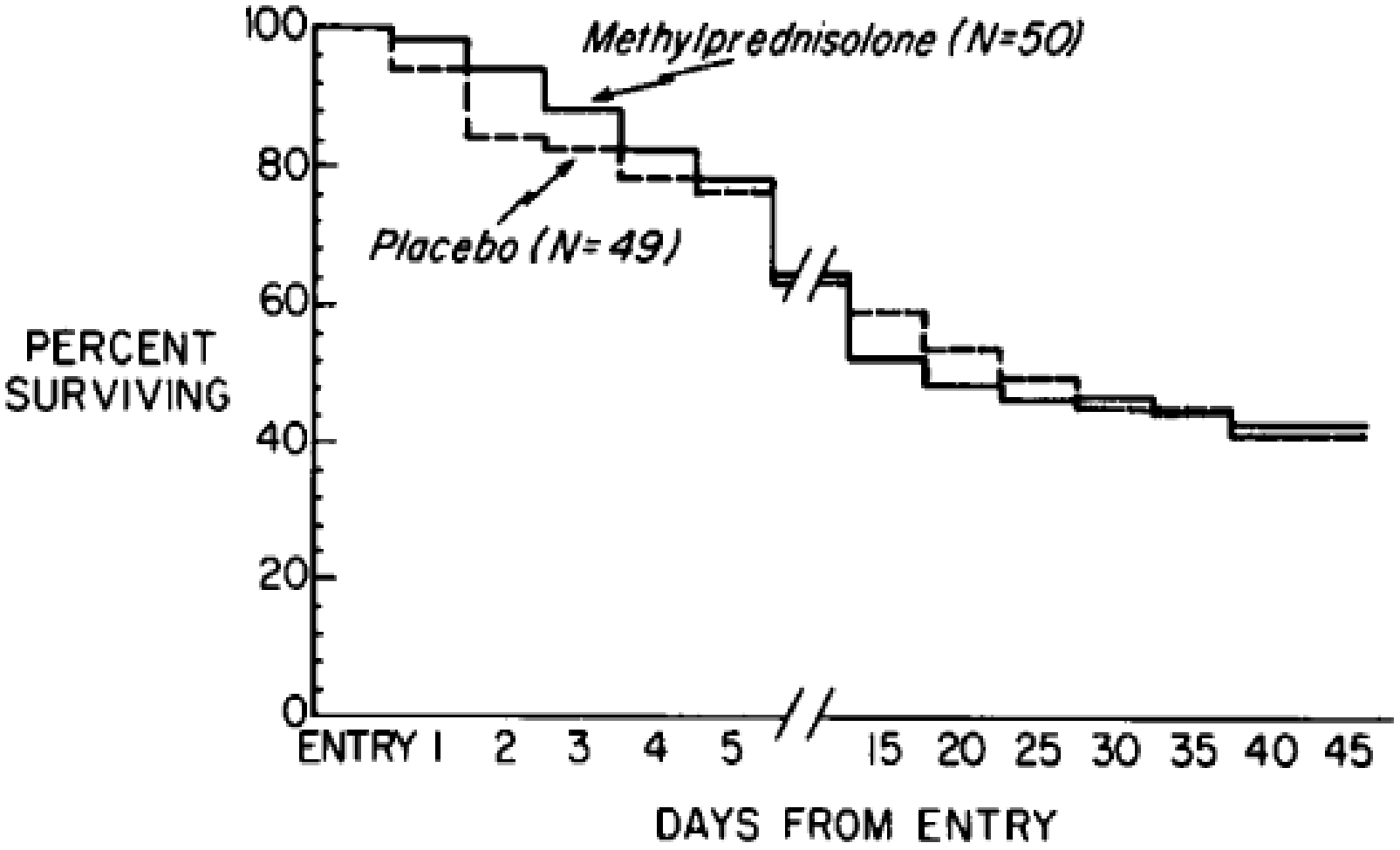
30mg/kg every 6 h for 1 day



N Engl J Med 1987;317:1565

High-dose Steroid Therapy in ARDS

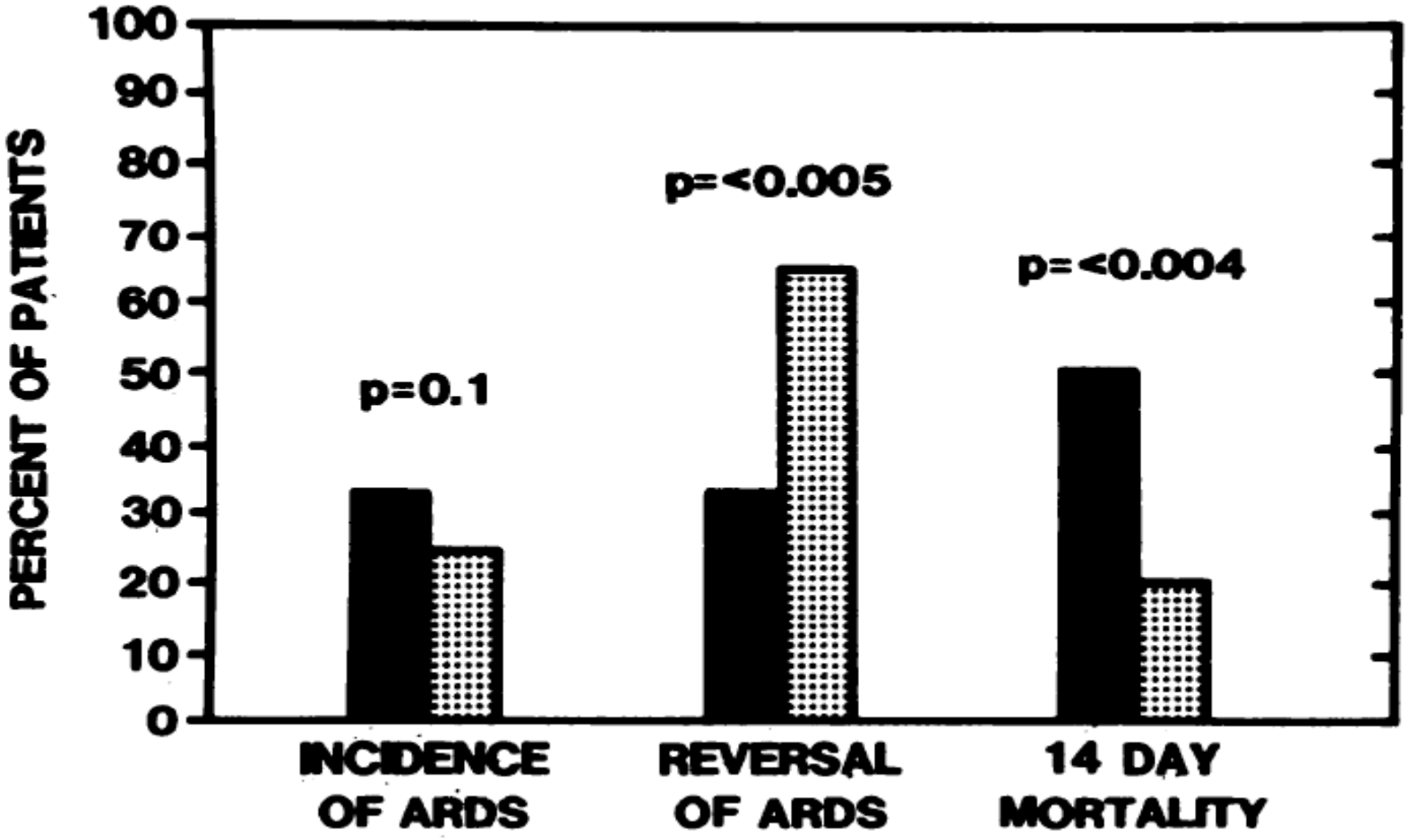
30mg/kg every 6 h for 1 day



N Engl J Med 1987;317:1565

High-dose Steroid Therapy in Septic ARDS

30mg/kg every 6 h for 1 day



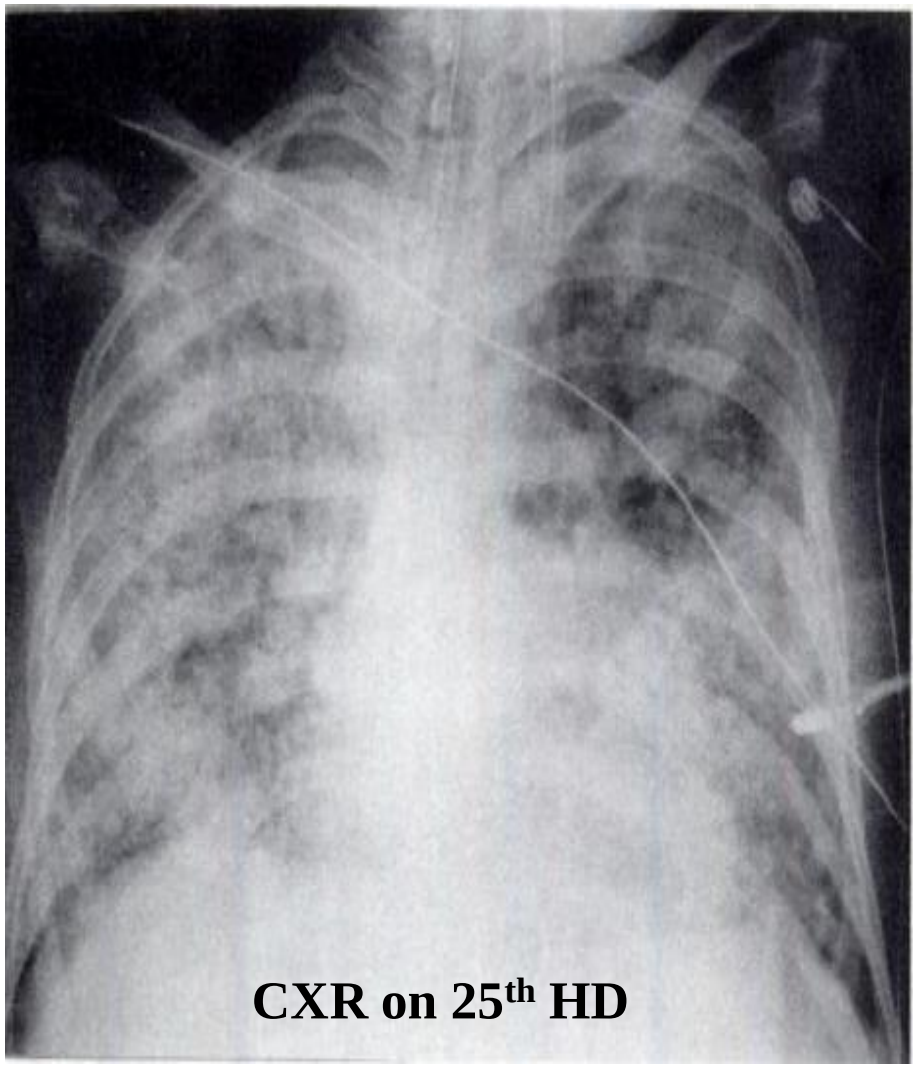
Chest 1987;92:1032

Sustained Course of Steroid for ARDS

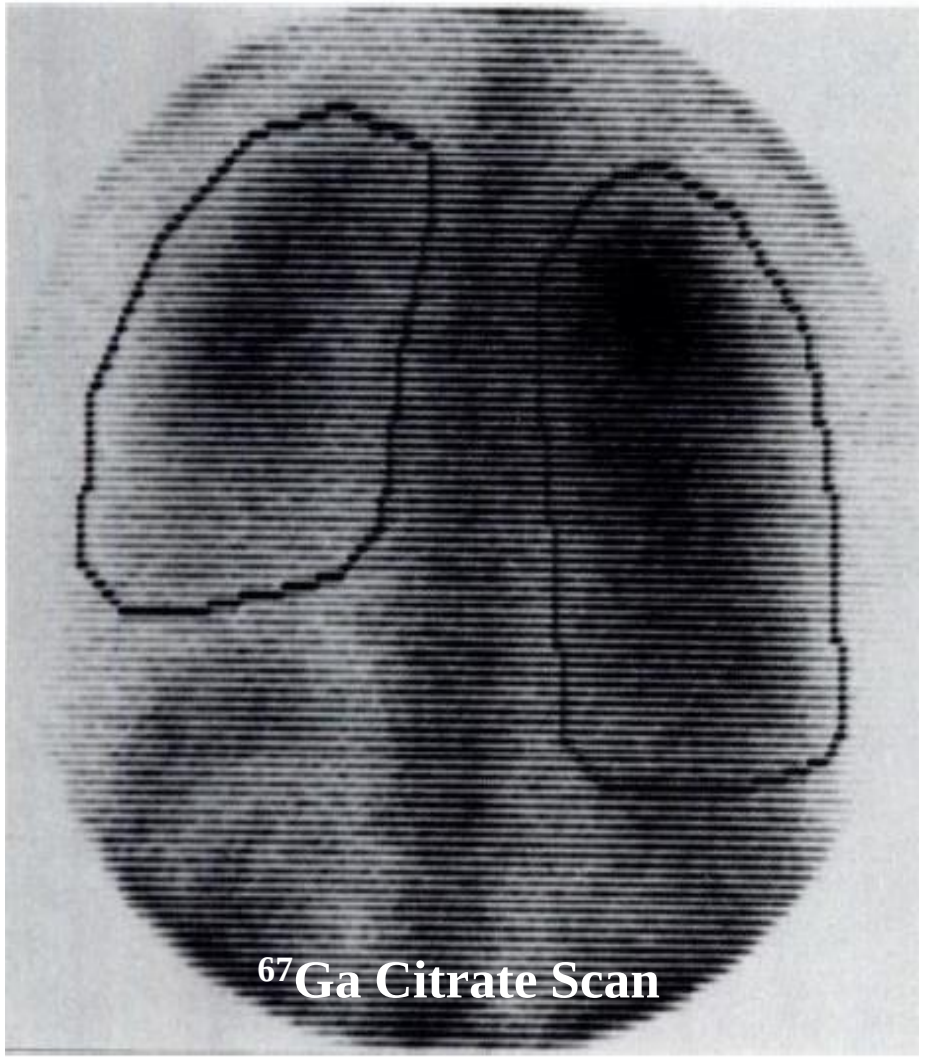
The word, "controversy," is repeatedly used to describe the debate surrounding the use of ACS in patients suffering from ARDS. Prominent clinicians and scientists are on opposite sides of the issue quoting well-done work to support their views.[1-6] Recent carefully performed studies have shown short-term, high-dose adrenocortical steroids do not improve ultimate outcome.[1,2] Our experience has led us to question further the use of these agents in this complicated problem. What is the effect of a longer course of therapy? Can patient selection identify a group or subset who may respond to this therapy? What are the implications of gallium uptake by ARDS lungs for pathogenesis and therapy?

Corticosteroid Tx in Late ARDS

Target for Active Inflammation



CXR on 25th HD

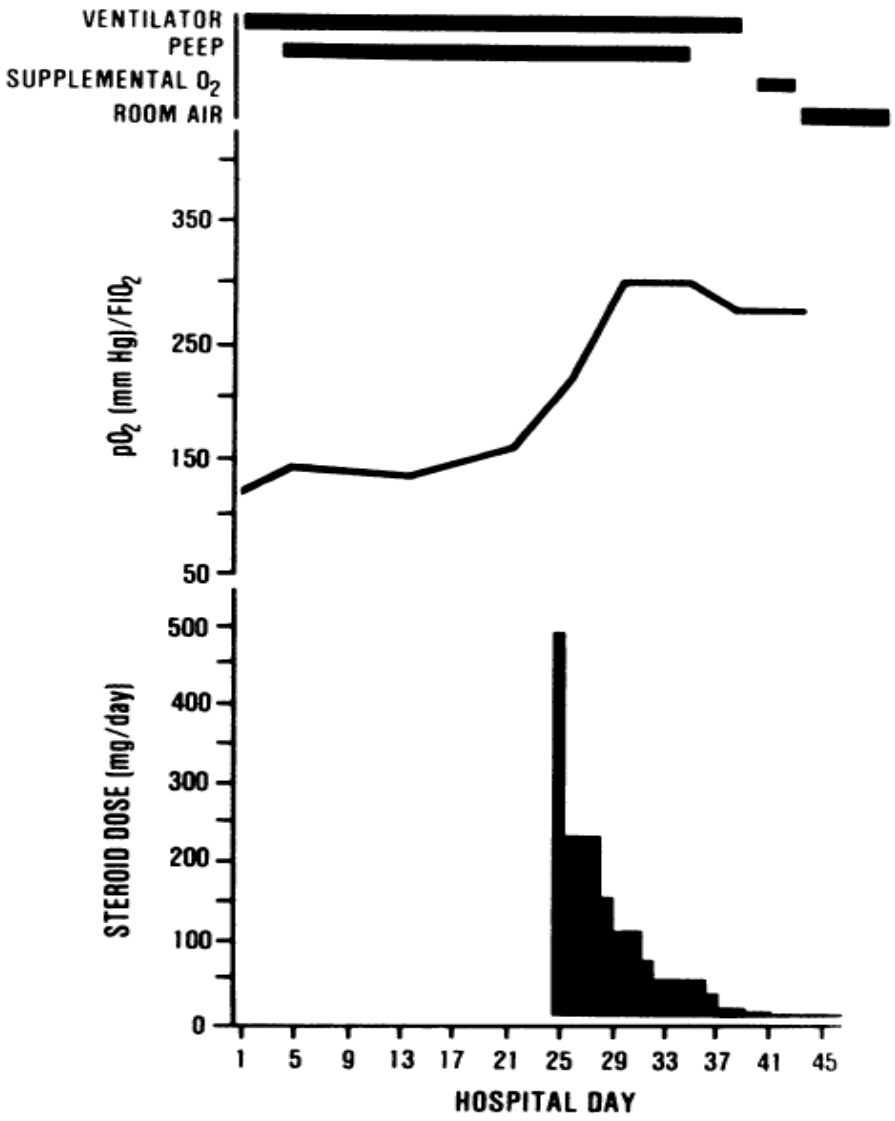


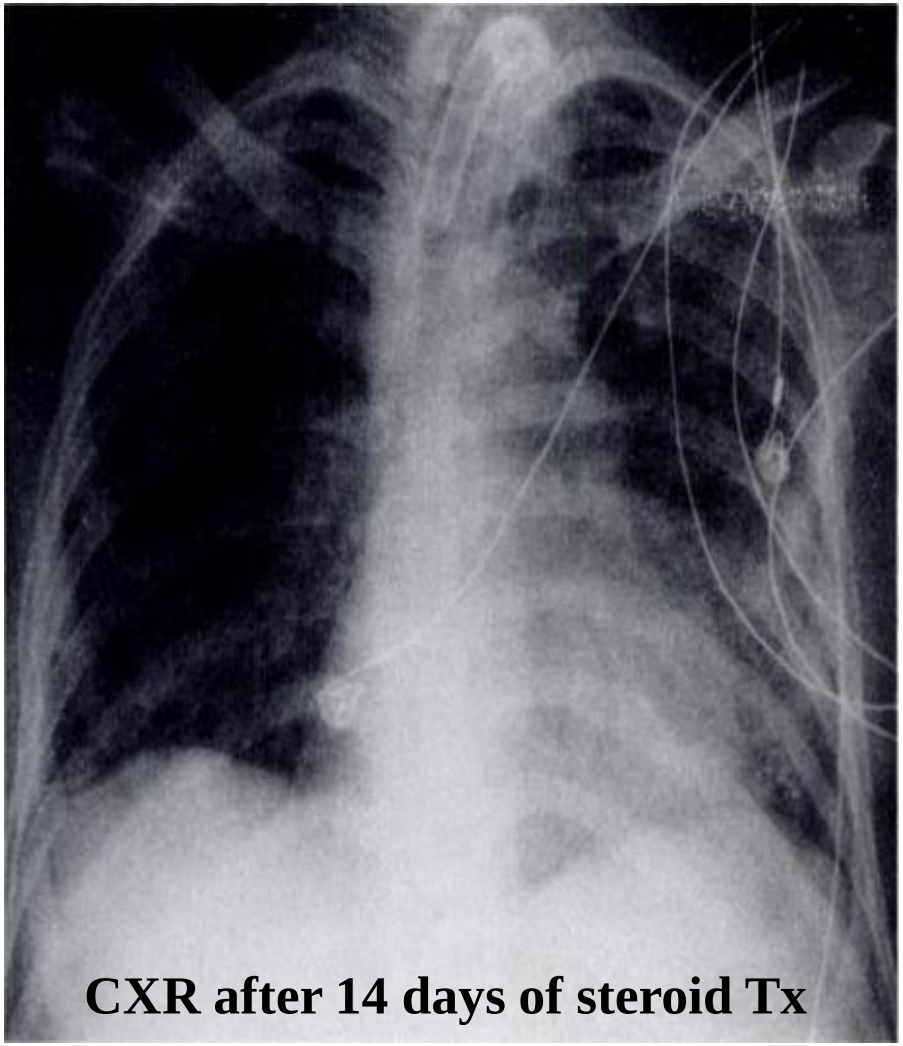
^{67}Ga Citrate Scan

Chest 1990;97:138

Corticosteroid Tx in Late ARDS

Representative Case



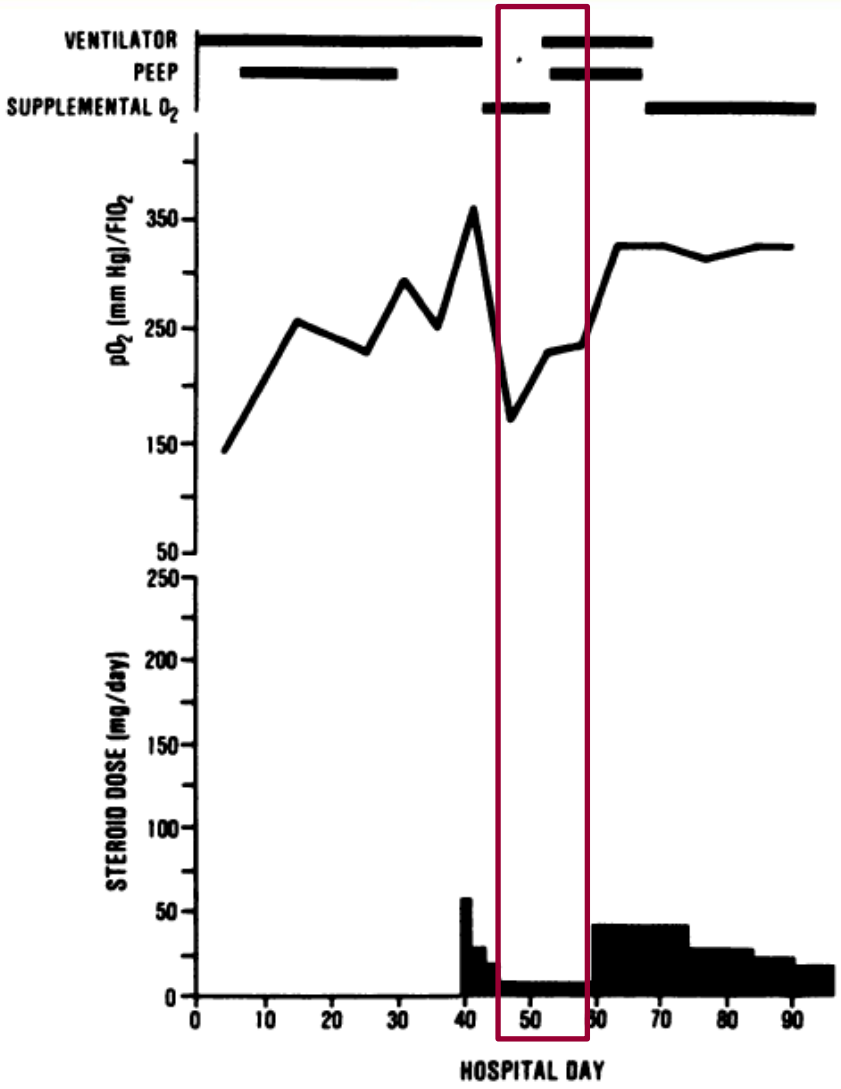


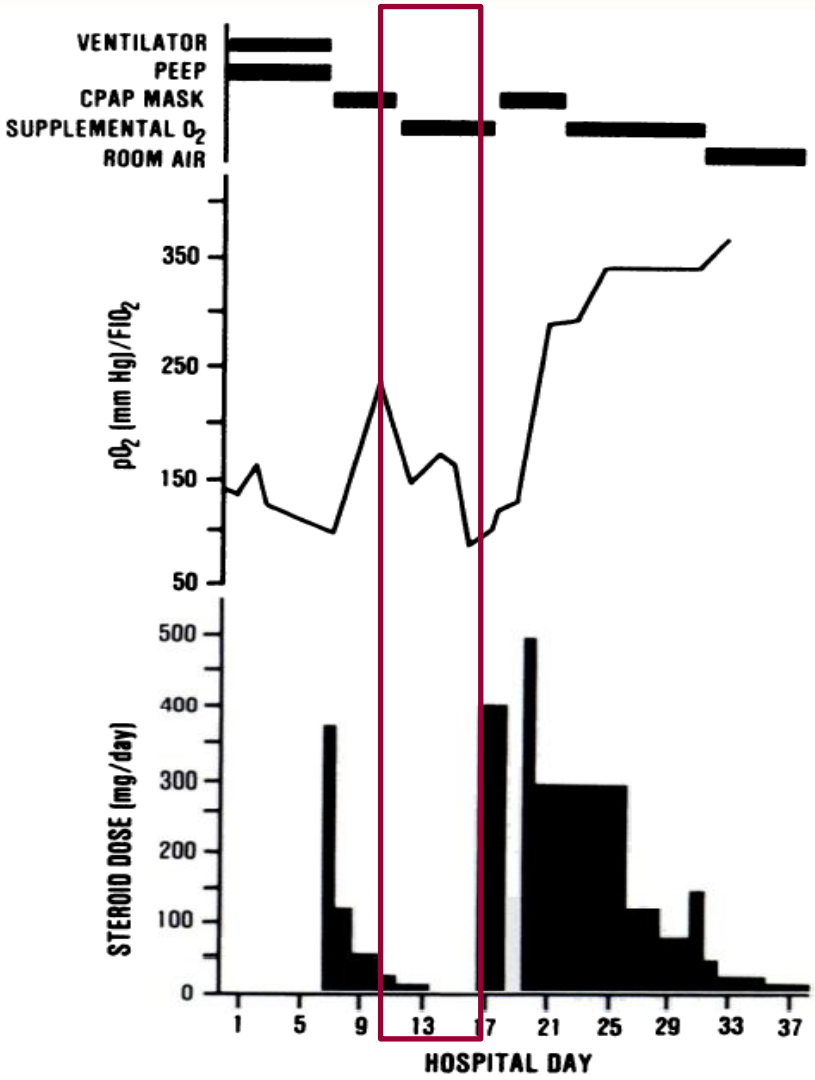
CXR after 14 days of steroid Tx

Chest 1990;97:138

Corticosteroid Tx in ARDS

Sustained Course of Steroid Treatment

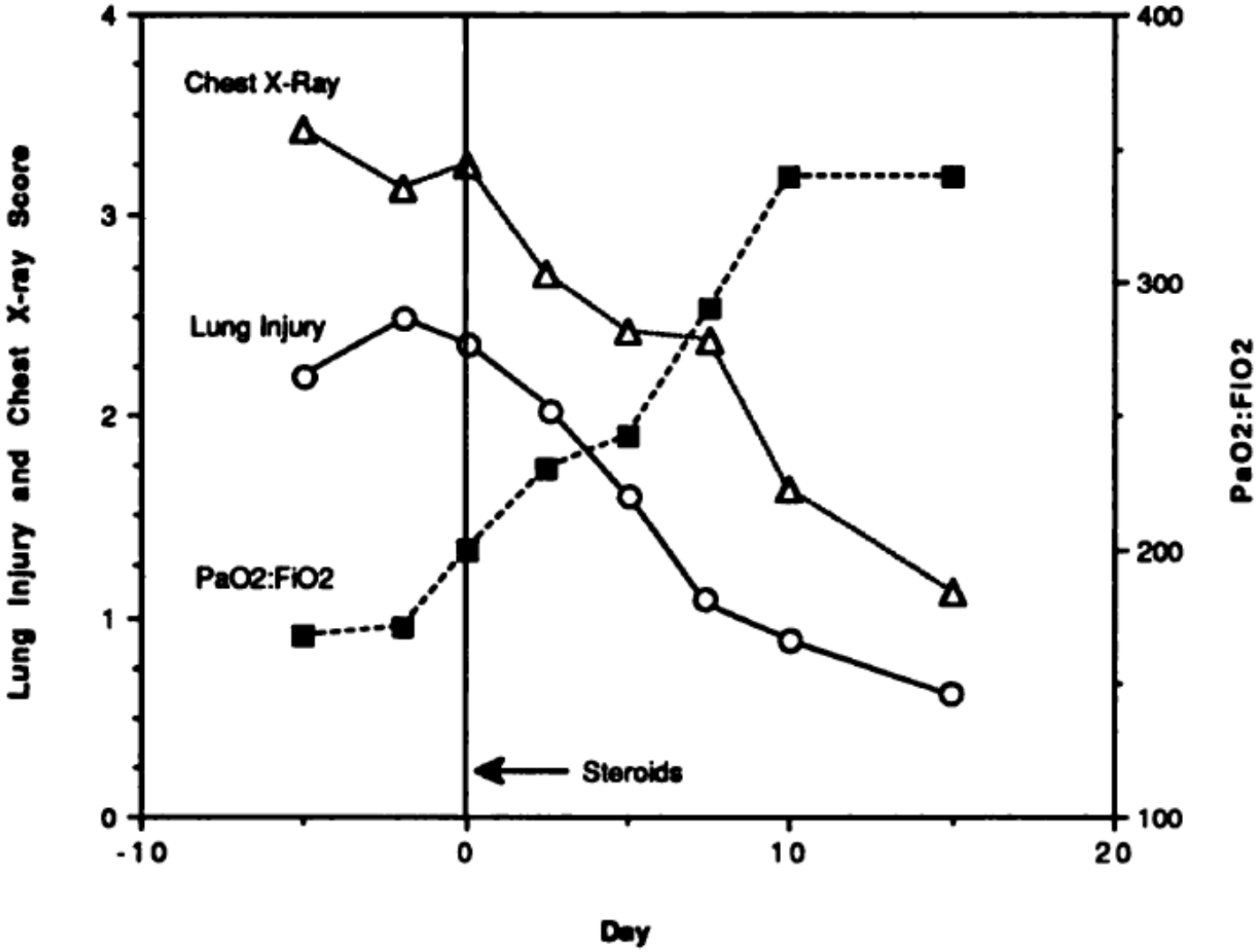




Chest 1990;97:138

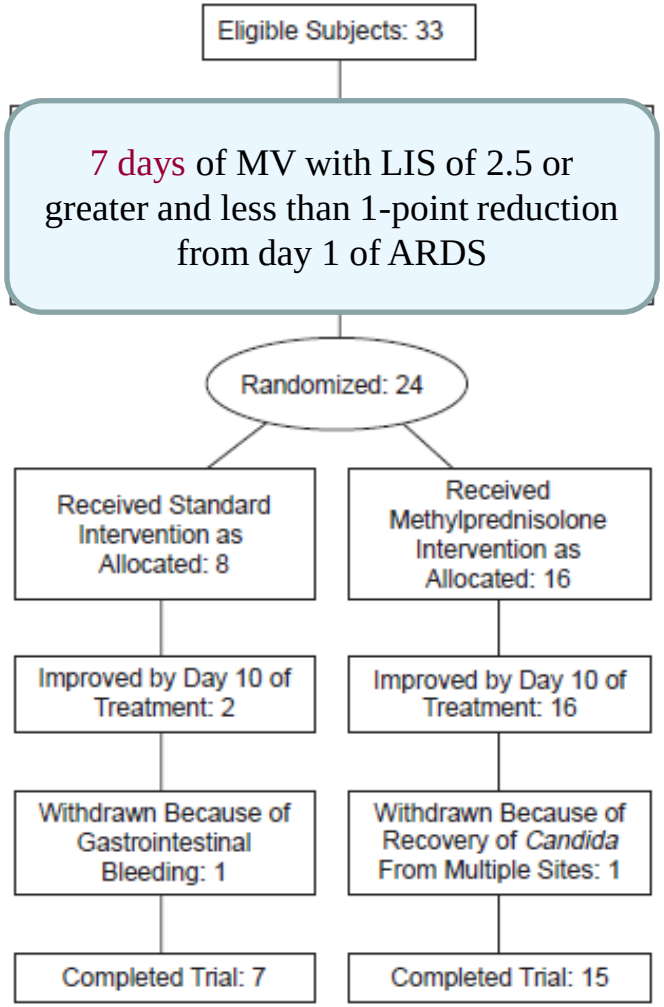
Effects of Sustained Course of Steroid Treatment

Case Series: Survival in 75%



Chest 1991;100:943

Prolonged, Moderate Dose of Steroid in ARDS
Multicenter RCT

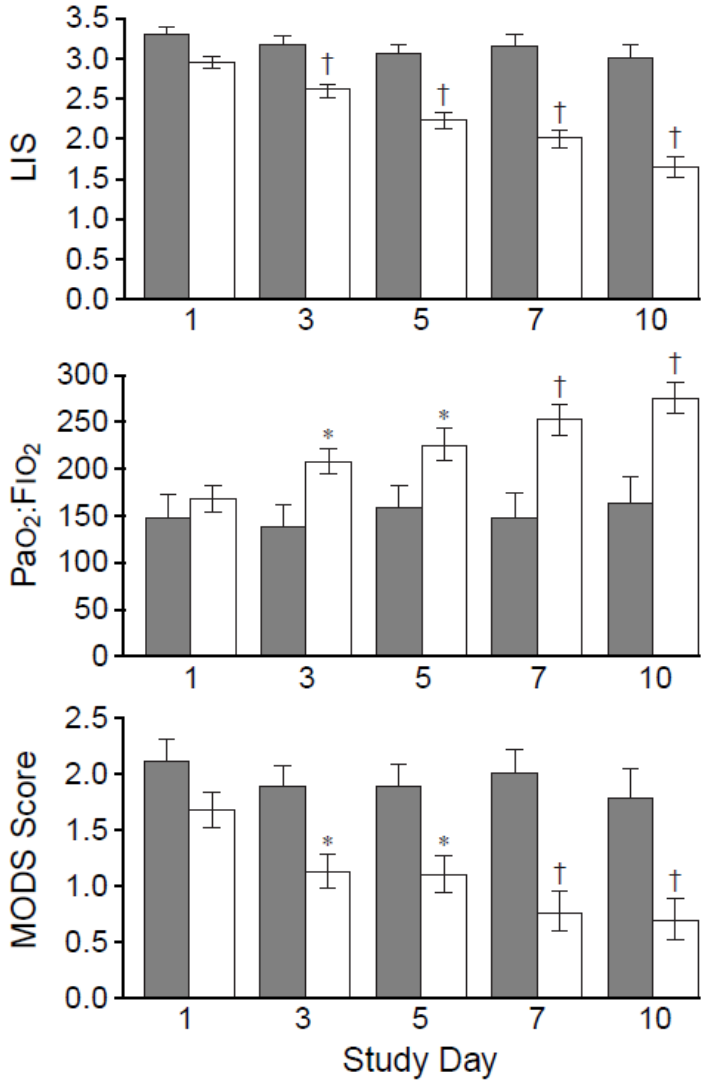


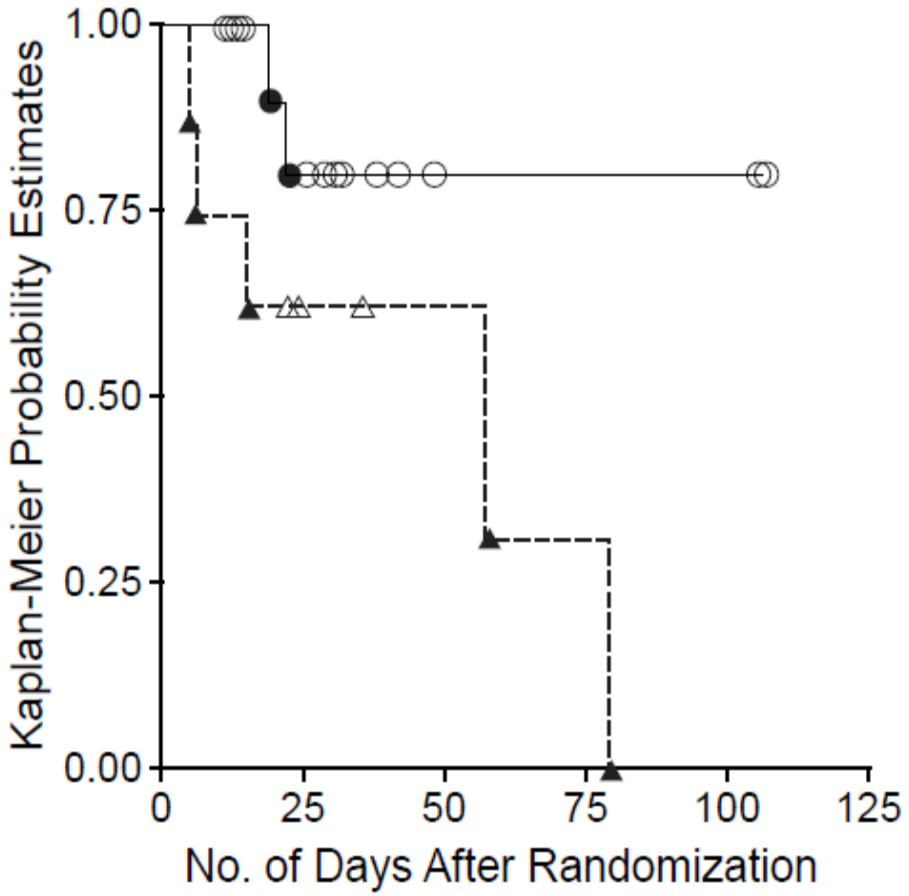
- Corticosteroid treatment
  - Loading dose 2mg/kg
  - D1~14: 2mg/kg/d
  - D15~21: 1mg/kg/d
  - D22~28: 0.5 mg/kg/d
  - D29~30: 0.25 mg/kg/d
  - D31~32: 0.125 mg/kg/d
  - If the patients was extubated prior to day 14, treatment was advanced to day 15 of drug therapy and tapered according to schedule

JAMA1998;280:159

Prolonged Corticosteroid in ARDS

Clinical Outcomes





JAMA 1998;280:159

Prolonged Corticosteroid in ARDS

Limitation: Different Baseline Characteristics

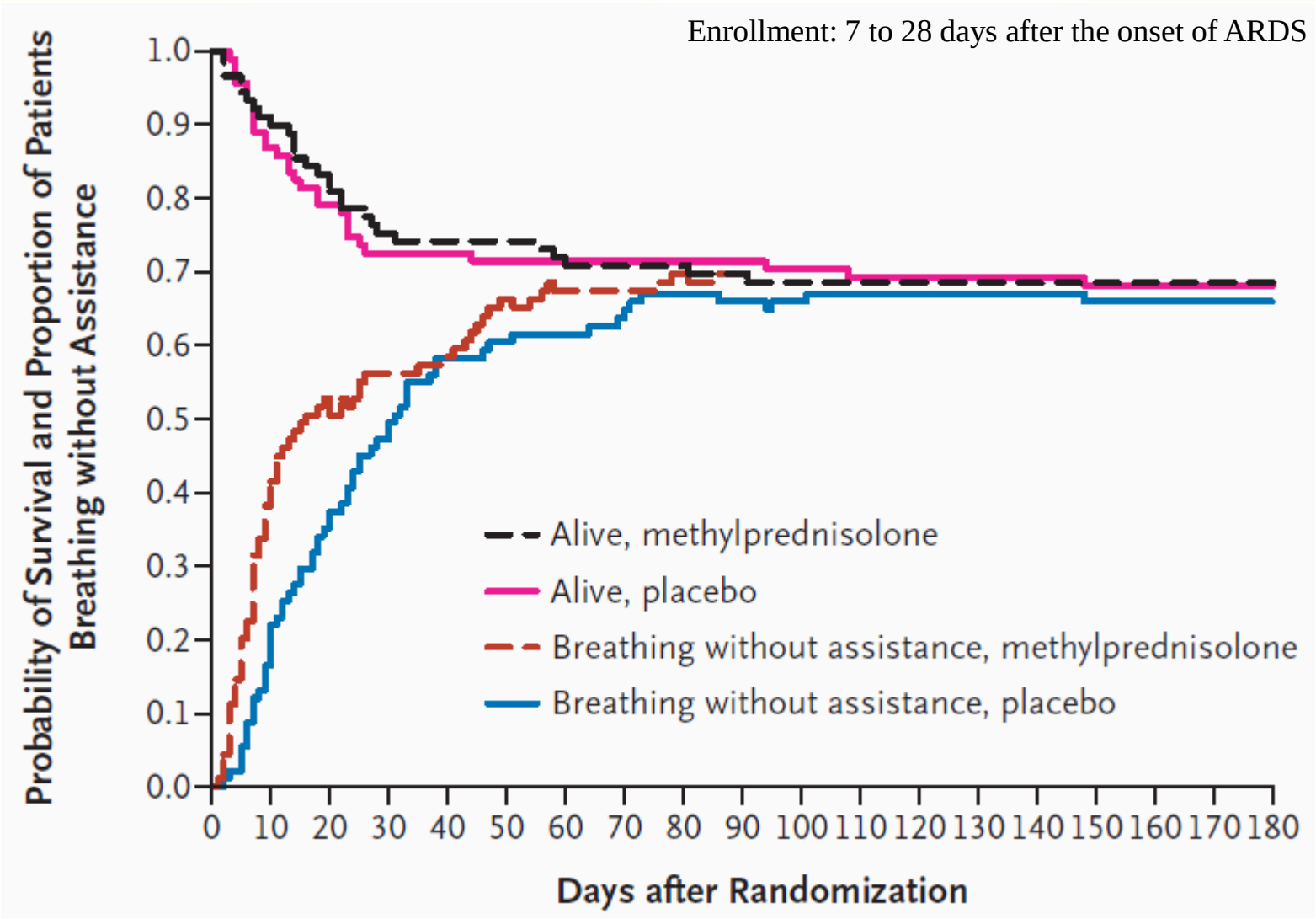
Characteristics	Methylprednisolone	Placebo	*P* Value
At Onset of ARDS			
No. of patients	16	8	NA
No. of male patients	5	4	.42
Age, mean (SEM), y	47 (3.9)	51 (6.6)	.58
APACHE III score, mean (SEM)†	58 (14)	55 (16)	.61
Direct cause of ARDS, No. (%)‡	9 (56)	6 (75)	.66
Presence of sepsis, No. (%)	12 (75)	5 (63)	.65
Presence of septic shock, No. (%)	10 (63)	3 (38)	.39
Ratio of PaO_2 to FIO_2, mean (SEM)	110 (11)	123 (11)	.30
Lung injury score, mean (SEM)	2.9 (0.1)	2.9 (0.1)	.77
MODS score, mean (SEM)	2.4 (0.3)	2.0 (0.3)	.37
At Study Entry			
No. of patients	16	8	NA
Duration of ARDS, mean (SEM), y	9.4 (0.9)	8.8 (1.2)	.70
Recent nosocomial infections, No. (%)§	8 (50)	2 (25)	.39
Temperature, mean (SEM), °C	37.3 (0.3)	37.8 (0.4)	.29
Pulmonary artery pressure, mean (SEM)	31 (4.1)	33 (3.2)	.53
Ratio of PaO_2 to FIO_2, mean (SEM)	161 (14)	141 (19)	.39
PEEP, mean (SEM), cm H_2O	12 (1.2)	14 (1.7)	.26
Lung injury score, median (IQR)	3.0 (2.5-3.4)	3.3 (3.0-3.6)	.16
MODS score, median (IQR)	1.5 (1.0-2.0)	2.5 (1.0-3.0)	.22
Presence of pneumothorax, No. (%)	5 (31)	2 (25)	.99

JAMA 1998;280:159

Moderate Dose of Steroid in ARDS

ARDS Clinical Trial Network

Enrollment: 7 to 28 days after the onset of ARDS



N Engl J Med 2006;354:1671

Prolonged Corticosteroid in Late ARDS

ARDS Clinical Trial Network

Characteristic	Total Population		Randomization within 7–13 Days after ARDS Onset		Randomization within 14–28 Days after ARDS Onset	
	Placebo (N=91)	Methyl-prednisolone (N=89)	Placebo (N=66)	Methyl-prednisolone (N=66)	Placebo (N=25)	Methyl-prednisolone (N=23)
Days from ARDS onset to study entry	11.3±4.0	11.3±3.8	9.3±2.0	9.4±2.0	16.6±3.0	16.6±2.4
Direct lung injury (%)†	56	54	62	52	40	61
Indirect lung injury (%)‡	44	46	38	48	60	39
APACHE III score§	84.6±29.4	87.6±27.5	86.8±31.6	87.9±28.4	78.8±22.2	86.9±25.3
PaO_2:FIO_2	126±40	126±42	125.4±42	124.6±44.7	125.5±34.4	128.4±34.6
No. of patients	86	84	63	62	23	22
Plateau pressure (cm of water)	33.8±9.7	34.5±10.0	33.2±8.1	34.4±9.5	35.2±13.1	35.0±11.7
No. of patients	65	66	47	51	18	15
Cstat‖	24.9±11.7	23.3±10.2	24.4±10.5	24.8±10.5	26.3±14.8	18.4±7.4
No. of patients	61	63	45	48	16	15
Lung Injury Score**	3.0±1.1	3.3±0.9	3.1±1.0	3.1±0.9	2.7±1.2	3.7±0.8
No. of patients	59	61	44	46	15	15

N Engl J Med 2006;354:1671

Prolonged Corticosteroid in Late ARDS

ARDS Clinical Trial Network

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
60-Day mortality (%)	28.6	29.2	1.0
95% CI	20.8–38.6	20.8–39.4	
No. of ventilator-free days at day 28	6.8±8.5	11.2±9.4	<0.001
No. of organ-failure–free days			
Cardiovascular failure	17.9±10.2	20.7±8.9	0.04
Coagulation abnormalities	22.1±8.6	22.2±8.3	0.84
Hepatic failure	21.4±10.2	21.2±10.2	0.70
Renal failure	21.4±10.2	22.8±8.7	0.36
No. of ICU-free days at day 28	6.2±7.8	8.9±8.2	0.02
No. of serious adverse events associated with myopathy or neuropathy	0	9	0.001
Suspected or probable pneumonia (%)	14	6	0.05
No. of episodes of shock/no. of patients	17/15	6/5	0.03
No. of serious infections/no. of patients	43/30	25/20	0.14
Amylase on day 7 (U/liter)	73±50	125±131	0.003
Glucose on day 7 (mg/dl)	144.0±61.8	158.7±64.4	0.14
60-Day mortality according to time from ARDS onset			
7–13 Days (%)	36	27	0.26
No. of patients	66	66	
>14 Days (%)†	8	35	0.02
No. of patients	25	23	

N Engl J Med 2006;354:1671

Comparison of Protocols
Meduri et al vs. ARDS Clinical Trial Network

Duration of ARDS before enrollment: 8.8 ~ 9.4 days

Meduri's protocol

Day of Treatment	Total Daily Dose of Methylprednisolone, mg/kg
1 (Loading dose)	2
1–14*	2
15–21	1
22–28	0.5
29–30	0.25
31–32	0.125

*In patients extubated prior to day 14, therapy was advanced to day 15 of the treatment algorithm and tapered according to schedule. Doses were given as 25% of total daily dose every 6 hours IV and changed to an equivalent single daily oral dose when possible.

Duration of ARDS before enrollment: 9.3 ~ 9.4 days

ARDS Net protocol

Day of Treatment	Total Daily Dose of Methylprednisolone, mg/kg
1 (Loading dose)	2
1–14	2 (0.5 q6h)
15–21*	1 (0.5 q12h)

*In patients who completed 21 days of treatment and still required mechanical ventilation, corticosteroids were tapered over 4 days. Treatment was tapered over 2 days in patients who were extubated for >48 hours prior to study day 21, developed disseminated fungal infections, or developed septic shock.

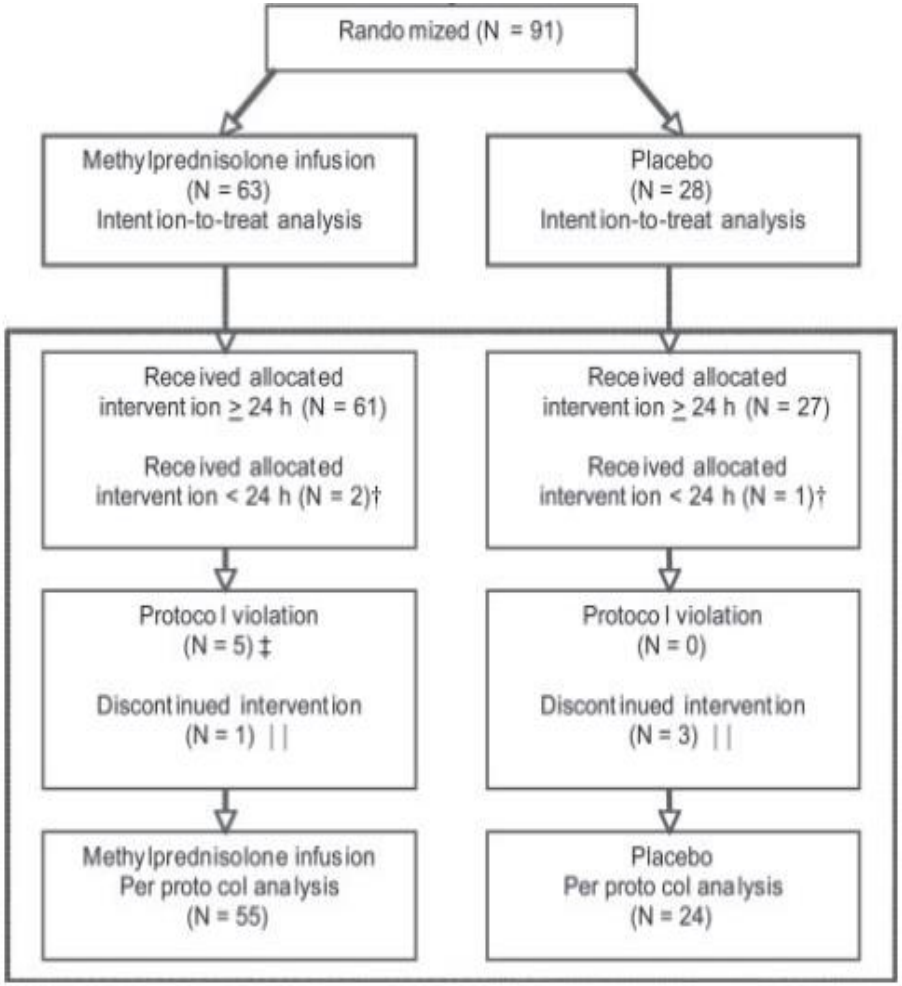
Low-Dose Corticosteroid in Septic Shock

Post-hoc Analysis for Early ARDS

	Nonresponders			Responders			All Patients		
	Placebo (n = 67)	Steroids (n = 62)	*p*	Placebo (n = 25)	Steroids (n = 23)	*p*	Placebo (n = 92)	Steroids (n = 85)	*p*
Day 28 mortality	50 (75)	33 (53)		12 (48)	16 (70)		62 (67)	49 (58)	
Unadjusted hazard ratio	0.60 (0.38–0.93)		.021	[a]		.360[b]	0.74 (0.51–1.08)		.123
Adjusted hazard ratio	0.57 (0.36–0.89)		.013	[a]		[a]	0.58 (0.39–0.85)		.005
Relative risk	0.71 (0.54–0.94)		.011	1.45 (0.89–2.36)		.130	0.86 (0.67–1.08)		.180
Adjusted odds ratio	0.35 (0.15–0.82)		.016	2.29 (0.49–10.64)		.290	0.48 (0.23–0.98)		.043
ICU mortality	53 (79)	36 (58)		14 (56)	17 (74)		67 (73)	53 (62)	
Relative risk	0.73 (0.57–0.94)		.010	1.32 (0.86–2.02)		.195	0.86 (0.70–1.05)		.136
Adjusted odds ratio	0.35 (0.15–0.82)		.016	1.80 (0.37–8.87)		.470	0.49 (0.24–0.99)		.046
Hospital mortality	53 (79)	37 (60)		14 (56)	17 (74)		67 (73)	54 (64)	
Relative risk	0.75 (0.59–0.96)		.016	1.32 (0.86–2.02)		.195	0.87 (0.71–1.07)		.184
Adjusted odds ratio	0.38 (0.16–0.88)		.025	1.80 (0.37–8.87)		.470	0.52 (0.26–1.06)		.072

Crit Care Med 2006;34:22

Early (≤ 72 h) Corticosteroid Therapy in ARDS

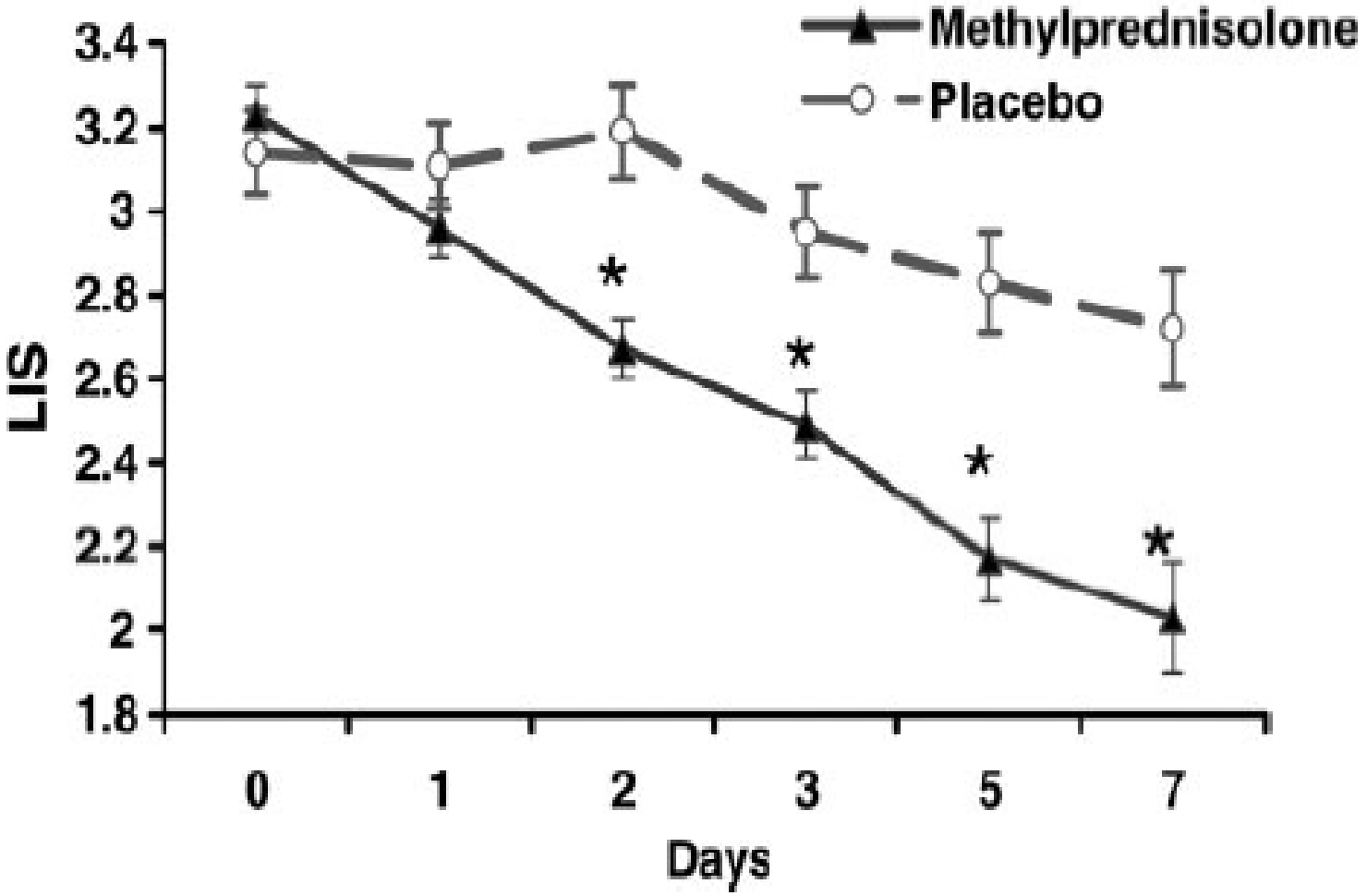


- Corticosteroid treatment within 72 h of diagnosis
  - Loading dose 1mg/kg
  - D1~14: 1mg/kg/d
  - D15~21: 0.5mf/kg/d
  - D22~25: 0.25 mg/kg/d
  - D26~28: 0.125 mg/kg/d
  - If the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to schedule

Chest 2007;131:954

Early (≤ 72 h) Corticosteroid Therapy in ARDS

Change of LIS over 7 Days



Chest 2007;131:954

Early (≤ 72 h) Corticosteroid Therapy in ARDS

Clinical Outcomes

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
Extubated or with ≥ 1-point reduction in LIS	44 (69.8)	10 (35.7)	1.96 (1.16–3.30)	0.002
Patients breathing without assistance	34 (54.0)	7 (25.0)	2.16 (1.09–4.26)	0.01
LIS† (mean ± SE)	2.14 ± 0.12	2.68 ± 0.14		0.004
Pao_2/FIo_2 ratio in ventilated patients (mean ± SE)	256 ± 19	179 ± 21		0.006
PEEP, cm H_2O	10.1 ± 4.6	12.9 ± 5.3		0.10
Mechanical ventilation-free days‡	2.2 ± 2.1	1.1 ± 1.9		0.02
MODS score†§	0.90 ± 1.1	1.9 ± 1.4		0.002
Patients with MODS score > 1	33 (54.1)	23 (85.2)	0.64 (0.48–0.84)	0.005
C-reactive protein level, mg/dL	2.9 ± 4.1	13.1 ± 6.8		< 0.0001
Cortisol level, µg/dL	5.7 ± 2.1	18.0 ± 1.6		< 0.0001
Patients with new infection‖	10 (15.9)	8 (28.6)	0.56 (0.25–1.26)	0.16
Patients with ventilator-associated pneumonia	4 (6.4)	6 (21.4)	0.30 (0.09–0.97)	0.06
Survivors	56 (88.9)	22 (78.6)	1.13 (0.92–1.40)	0.21
Patients with unresolving ARDS treated with open-label methylprednisolone at 2 mg/kg/d¶	5 (7.9)	10 (35.7)	0.22 (0.08–0.59)	0.002
Duration of mechanical ventilation, d†	5 (3–8)	9.5 (6–19.5)		0.002
Mechanical ventilation-free days to day 28‡	16.5 ± 10.1	8.7 ± 10.2		0.001
Length of ICU stay, d	7 (6–12)	14.5 (7–20.5)		0.007
Survivors of ICU admission	50 (79.4)	16 (57.4)	1.39 (0.98–1.96)	0.03
Length of hospital stay	13.0 (8–21)	20.5 (10.5–40.5)		0.09
Survivors of hospital admission	48 (76.2)	16 (57.1)	1.33 (0.94–1.89)	0.07

Chest 2007;131:954

Hydrocortisone for Early Septic ARDS

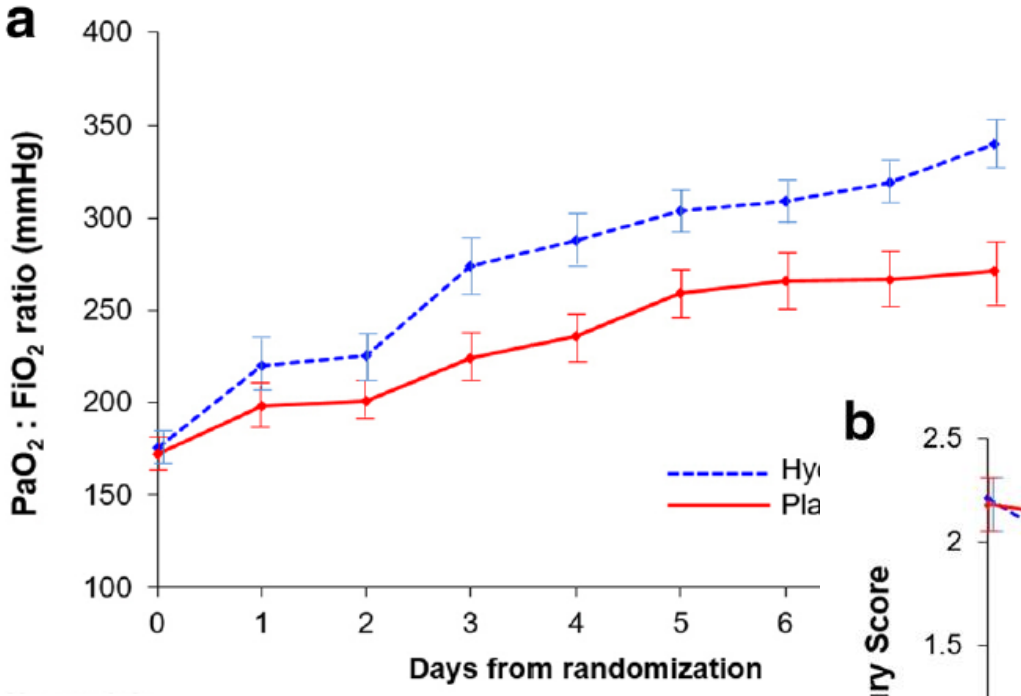
7 Day Course of Hydrocortisone (50 mg q 6 h)

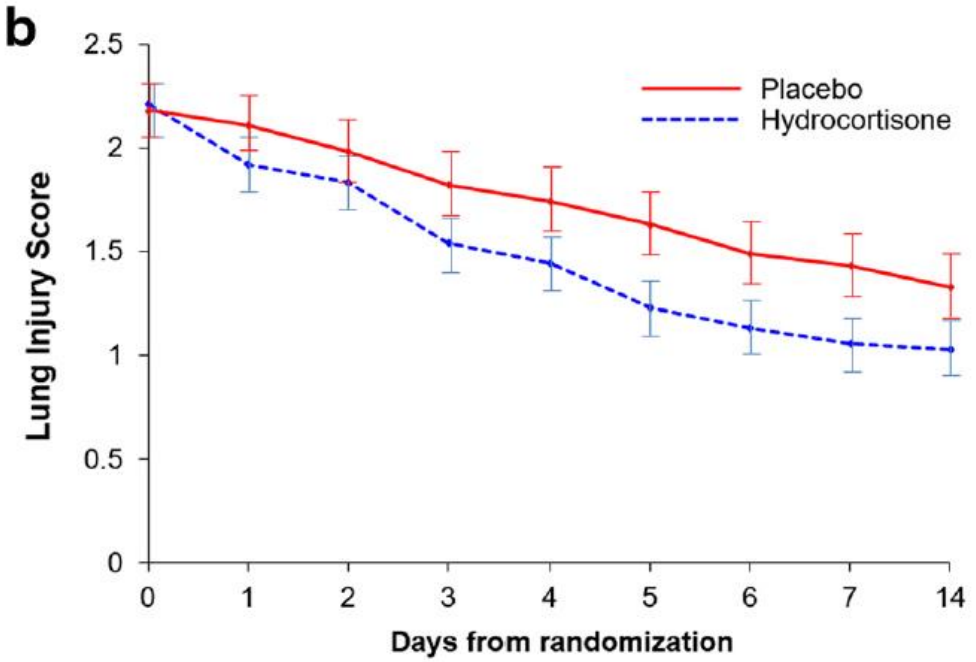
	Hydrocortisone ($n = 98$)	Placebo ($n = 99$)	Relative risk (95 % CI)	p Value[a]
Primary outcome				
Mortality at 28 days, *n* (%)	22 (22.5)	27 (27.3)	0.82 (0.50–1.34)	0.51
Secondary outcomes				
Mortality at 60 days, *n* (%)	34 (34.7)	40 (40.4)	0.86 (0.60–1.23)	0.46
Duration of mechanical ventilation up to day 28, days	11.8 ± 7.8	13.9 ± 9.0		0.17
Mechanical ventilation-free days to day 28	12.0 ± 9.7	9.7 ± 10.0		0.17
Duration of vasopressor treatment,[b] days	4.8 ± 3.0	6.8 ± 5.7		0.16
Renal replacement therapy, *n* (%)	22 (22.4)	22 (22.2)	1.01 (0.86–1.16)	1.00
Duration of renal replacement therapy dependent,[c] days	8.1 ± 6.6	8.2 ± 5.2		0.94
Alive on day 28 without organ support, *n* (%)	64 (65.3)	55 (55.6)	1.18 (0.94–1.48)	0.19
Organ support-free days to day 28[d]	11.9 ± 9.7	9.5 ± 9.8		0.13

Crit Care 2016;20:329

Hydrocortisone for Early Septic ARDS

7 Day Course of Hydrocortisone (50 mg q 6 h)





Crit Care 2016;20:329

Dexamethasone in Moderate to Severe ARDS

DEXA-ARDS Study, Spain

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

*Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luís A Conesa, Carmen Martín-Rodríguez, Francisco J Díaz-Domínguez, Pablo Serna-Grande, Rosana Rivas, José Ferreres, Javier Belda, Lucía Capilla, Alec Tallet, José M Añón, Rosa L Fernández, Jesús M González-Martín for the dexamethasone in ARDS network**

- Potent anti-inflammatory and weak mineralocorticoid effects compared with other corticoids
  - 20~30 times more potent than the naturally occurring hormone cortisol
  - 4~5 times more potent than prednisone
- Long lasting, allowing for a regimen of one dose per day

Lancet 2011; 377: 2023

- 10 days of administration: 20 mg once daily from day 1 to day 5, and then reduced to 10 mg once daily from day 6 to day 10.

Time of Enrollment
DEXA-ARDS Study, Spain

	Dexamethasone group (n=139)	Control group (n=138)
Age, years	56 (14)	58 (15)
Sex		
Female	43 (31%)	43 (31%)
Male	96 (69%)	95 (69%)
Sequential Organ Failure Assessment score*	8·7 (3·1)	8·6 (3·2)
Time from intubation to randomisation, days	2·1 (2·6)	2·1 (2·6)
Time from ARDS diagnosis to randomisation, days	1·0 (0·1)	1·0 (0·2)
Cause of ARDS		
Pneumonia	75 (54%)	72 (52%)
Sepsis	33 (24%)	34 (25%)
Aspiration	18 (13%)	15 (11%)
Trauma	11 (8%)	10 (7%)
Others	2 (1%)	7 (5%)
Degree of lung severity, number of patients		
Moderate (100 <PaO_2/FiO_2 ≤200)	118	121
Severe (PaO_2/FiO_2 ≤100)	21	17
PaO_2/FiO_2, mm Hg	142·4 (37·3)	143·5 (33·4)

Lancet Respir Med 2020;8:267

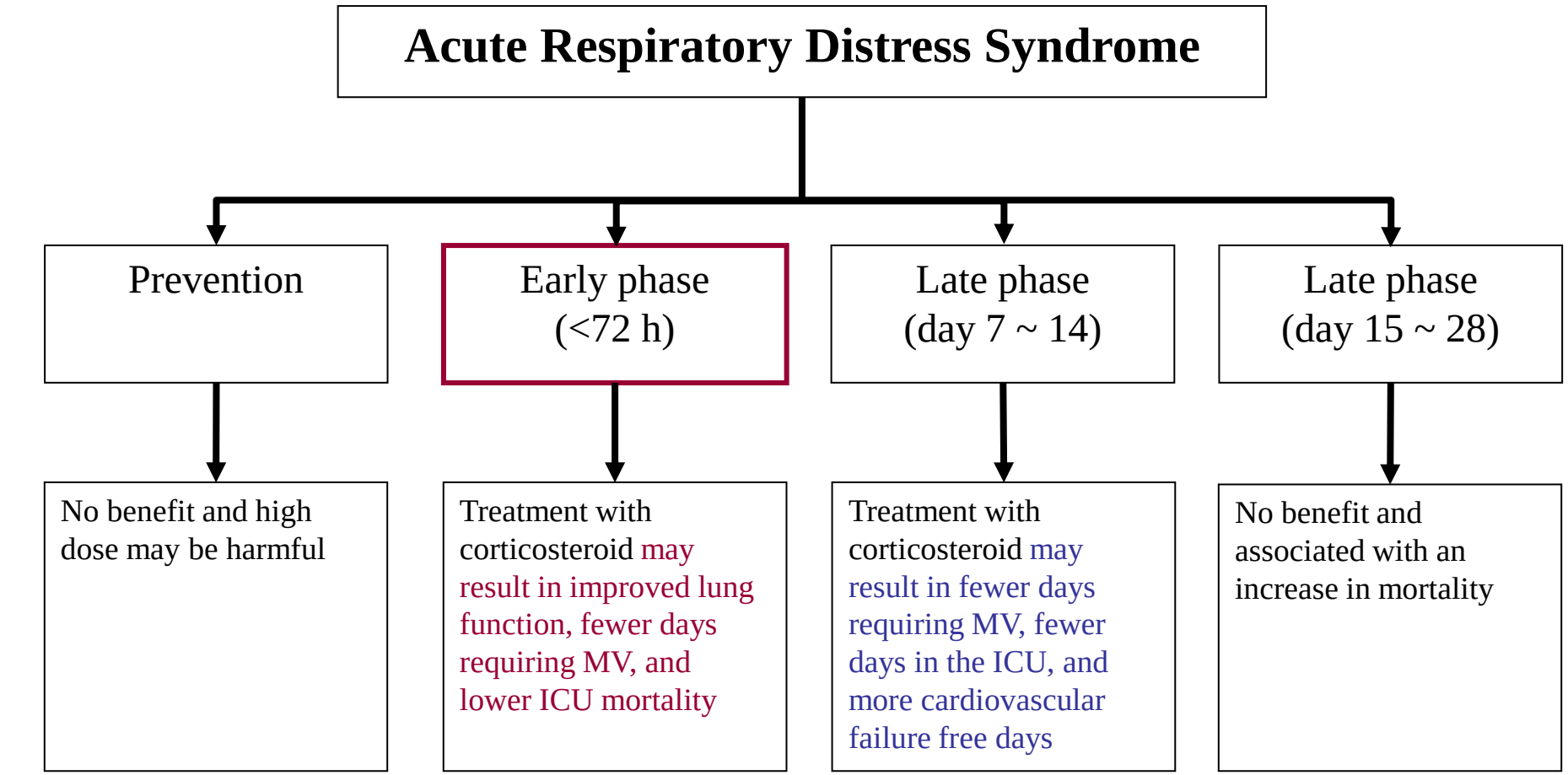
Clinical Outcomes
DEXA-ARDS Study, Spain

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12·3 (9·9)	7·5 (9·0)	4·8 (2·57 to 7·03)	<0·0001
All-cause mortality at day 60	29 (21%)	50 (36%)	−15·3% (−25·9 to −4·9)	0·0047
ICU mortality	26 (19%)	43 (31%)	−12·5% (−22·4 to −2·3)	0·0166
Hospital mortality	33 (24%)	50 (36%)	−12·5% (−22·9 to −1·7)	0·0235
Actual duration of mechanical ventilation in ICU survivors, days	14·2 (13·2)	19·5 (13·2)	−5·3 (−8·4 to −2·2)	0·0009
Actual duration of mechanical ventilation in survivors at day 60, days	14·3 (13·3)	20·2 (14·0)	−5·9 (−9·1 to −2·7)	0·0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5·2% (−5·2 to 15·6)	0·33
New infections in ICU	33 (24%)	35 (25%)	1·6% (−8·5 to 11·7)	0·75
Barotrauma	14 (10%)	10 (7%)	2·8% (−4·0 to 9·8)	0·41

Lancet Respir Med 2020;8:267

Steroid Therapy in ARDS

Evidence on Timing



Costicosteroid for Early ARDS

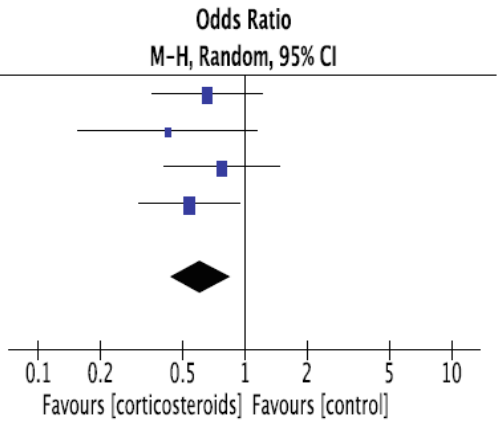
Meta-analysis of 4 RCTs

All-cause 28- or 30-day mortality

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Annane 2006	49	85	62	92	29.1%	0.66 [0.36, 1.22]	2006
Meduri 2007	12	63	10	28	11.0%	0.42 [0.16, 1.15]	2007
Tongyoo 2016	22	98	27	99	26.0%	0.77 [0.40, 1.48]	2016
Villar 2020	25	139	40	138	33.9%	0.54 [0.30, 0.95]	2020
Total (95% CI)		**385**		**357**	**100.0%**	**0.61 [0.44, 0.85]**	
Total events	108		139				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.27$, df = 3 (P = 0.74); $I^2 = 0\%$

Test for overall effect: Z = 2.93 (P = 0.003)

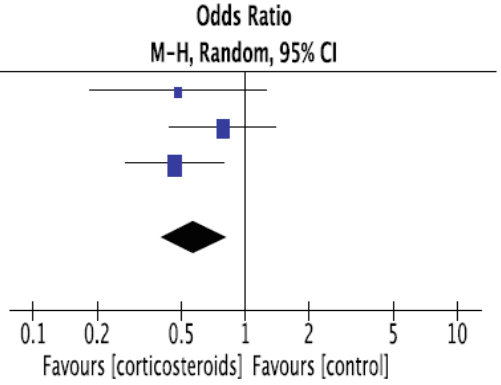


All-cause 60-day mortality

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Meduri 2007	15	63	11	28	14.5%	0.48 [0.19, 1.25]	2007
Tongyoo 2016	34	98	40	99	39.6%	0.78 [0.44, 1.40]	2016
Villar 2020	29	139	50	138	45.9%	0.46 [0.27, 0.79]	2020
Total (95% CI)		**300**		**265**	**100.0%**	**0.57 [0.40, 0.83]**	
Total events	78		101				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.84$, df = 2 (P = 0.40); $I^2 = 0\%$

Test for overall effect: Z = 2.99 (P = 0.003)



J Intensive Care 2020;8:91

Timing and Duration of Corticosteroid Tx

Back to the Past

Table 1—*Patient Experience: Established ARDS Treated with Sustained ACS*

Case No.	ARDS Classification*	Duration of ARDS, Days	ACS Therapy, Days: Total Duration	ACS Therapy, Days: Dose/(Mg/Day) >240	ACS Therapy, Days: Dose/(Mg/Day) >40	^{67}Ga: Computer Ratio	^{67}Ga: Visual Score	Outcome
1	Isolated	40	150	None	19	. . .	2	Survived
2	Complicated	7	28	10	20	1.7	3	Died
						1.95	2	
3	Isolated	25	21	4	13	. . .	. . .	Survived
4	Isolated	7	28	2	5	. . .	3	Survived
5	Isolated	3	21	4	10	2.41	3	Survived
6	Complicated	4	14	5	14	3.9	3	Died
7	Complicated	5	28	3	8	1.86	2	Survived
8	Isolated	3	22	4	7	7.79	2	Survived
9	Complicated	8	37	4	12	. . .	. . .	Survived
10	Complicated	9	30	4	14	1.46	2	Survived

Chest 1990;97:138

Corticosteroid for ARDS

CONFERENCE REPORTS AND EXPERT PANEL

Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Djillali Annane[1*], Stephen M. Pastores[2*], Bram Rochwerg[3], Wiebke Arlt[4], Robert A. Balk[5], Albertus Beishuizen[6], Josef Briegel[7], Joseph Carcillo[8], Mirjam Christ-Crain[9], Mark S. Cooper[10], Paul E. Marik[11], Gianfranco Umberto Meduri[12], Keith M. Olsen[13], Sophia Rodgers[14], James A. Russell[15] and Greet Van den Berghe[16]

ECCM & ESICM Recommendation, 2017

- In summary, the task force suggested that methylprednisolone be considered in patients with early (up to day 7 of onset; PaO2/FiO2 of <200) in a dose of 1 mg/kg/day and late (after day 6 of onset) persistent ARDS in a dose of 2 mg/kg/day followed by slow tapering over 13 days
- Methylprednisolone is suggested because of its greater penetration into lung tissue and longer residence time.
- Furthermore, methylprednisolone should be weaned slowly (6–14 days) and not stopped rapidly (2–4 days) or abruptly as deterioration may occur from the development of a reconstituted inflammatory response.
- Finally, glucocorticoid treatment blunts the febrile response; therefore, infection surveillance is recommended to ensure prompt identification and treatment of hospital-acquired infections.

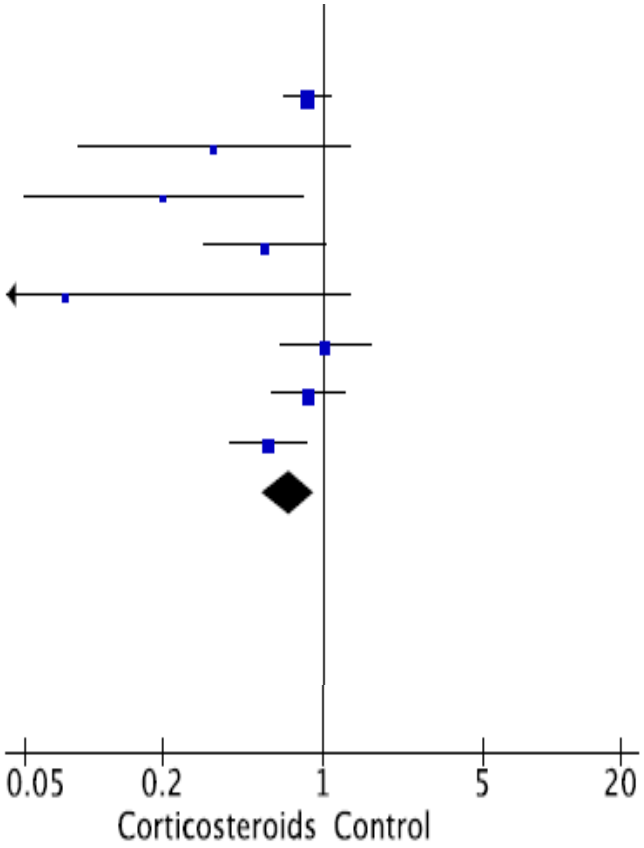
Intensive Care Med 2017; 43:1751

Systematic Review on Steroid Therapy in ARDS

1.20.2 Non Covid 19						
Annane 2006	49	85	62	92	21.6%	0.86 [0.68, 1.08]
Liu 2012	2	12	7	14	2.0%	0.33 [0.08, 1.31]
Meduri 1998	2	16	5	8	1.9%	0.20 [0.05, 0.81]
Meduri 2007	15	63	12	28	7.9%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	0.5%	0.08 [0.00, 1.32]
Steinberg 2006	26	89	26	91	11.8%	1.02 [0.65, 1.62]
Tongyoo 2016	34	98	40	99	15.3%	0.86 [0.60, 1.23]
Villar 2020	29	139	50	138	14.0%	0.58 [0.39, 0.85]
Subtotal (95% CI)		**520**		**479**	**74.9%**	**0.71 [0.54, 0.92]**
Total events	157		205			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 13.33$, df = 7 (P = 0.06); $I^2 = 47\%$

Test for overall effect: Z = 2.60 (P = 0.009)



Intensive Care Med 2021;47:521

Adverse Events of Corticosteroids
Prolonged Treatment

- Critical illness polymyoneuromyopathy (weakness)
  - Increased severity of neuromyopathy
- Hyperglycemia
- Gastrointestinal bleeding
- Risk of secondary infection
  - Increased incidence of bacterial superinfection
  - Associated with opportunistic infection

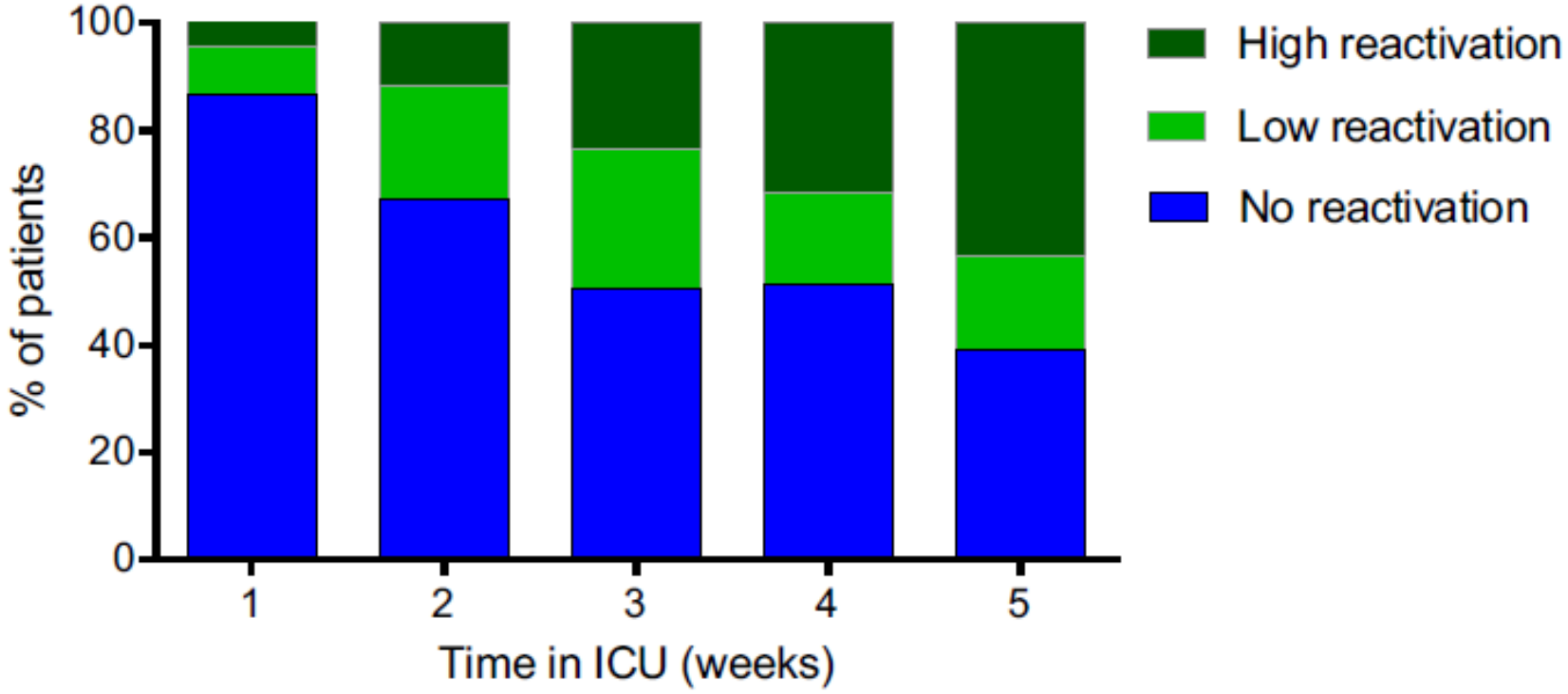
N Engl J Med 2008;358:111

Pharmacotherapy 2022;42:71

▶Associated with poor outcomes: may compensate the positive effect of prolonged corticosteroid treatment

CMV Reactivation in ARDS

MARS Cohort, Netherland



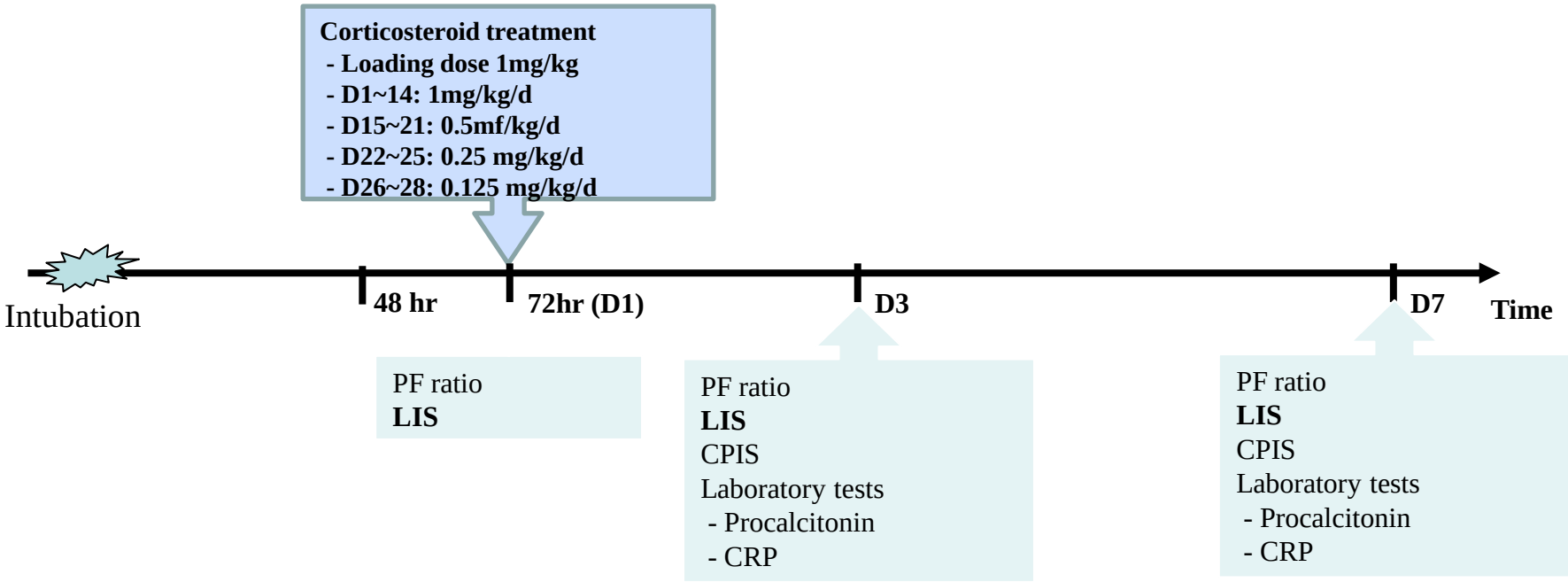
▶ CMV reactivation was associated with overall increased ICU mortality (adjusted subdistribution hazard ratio (SHR) 2.74, 95 % CI 1.51–4.97)

Intensive Care Med 2016;42:333

Evaluation of Responsiveness at Day 7

- Responsiveness to corticosteroid treatment at 7 days
  - Weaning from MV within 7 days after treatment
  - Improvement in lung function defined as follows
    - Reduction in lung injury score (LIS) ≥ 1 point
    - LIS at 7-day ≤ 2.0 (for study entry LIS ≤ 2.9) or ≤ 2.5 (for study entry LIS ≥ 3.0)

Chest 2007;131:954



Yonsei Med J 2015;56:287

Comparisons of Clinical Outcomes
Responders vs. Non-responders

Characteristics	Responders (n = 10)	Nonresponders (n = 10)	P value
Clinical outcomes			
ICU mortality	1 (10)	8 (80)	0.005
Length of stay in ICU, days	8.5 (7.0 – 20.0)	21.5 (17.0 – 28.0)	0.089
In-hospital mortality	3 (30)	9 (90)	0.020
Severity of ARDS			
Lung injury score	3.0 (2.7 – 3.3)	2.9 (2.8 – 3.0)	0.631
PF ratio	170.5 (149.4 – 192.8)	127.2 (117.1 – 143.8)	0.023
NT-proBNP, pg/mL	2094 (921 – 5572)	5478 (713 – 17489)	0.529
Procalcitoin, ng/mL	0.51 (0.29 – 1.80)	0.61 (0.39 – 1.27)	0.853
CRP	18.8 (14.7 – 21.9)	15.7 (10.9 – 24.9)	0.631
Serum TGF-ß, pg/mL	4326.9 (3098.7 – 11358.5)	3451.7 (15.5 – 12220.5)	0.684
Serum IL-6, pg/mL	87.3 (26.2 – 385.1)	134.2 (47.5 – 210.4)	0.739
Serum TNF-α, pg/mL	13.7 (12.2 – 18.7)	12.6 (10.8 – 18.6)	0.796
BAL TREM-1, pg/mL	313.6 (208.9 – 329.8)	520.5 (368.8 – 697.8)	0.029
BAL procollagen, ng/mL	14.5 (11.8 – 27.9)	26.3 (11.6 – 73.5)	0.280
Changes at day 2 after treatment			
Change in LIS	-1.0 (-1.0 – -0.8)	0 (-0.3 – 0)	<0.001
Change in PF ratio	44.0 (3.4 – 52.8)	-3.7 (-18.8 – 43.0)	0.278

Yonsei Med J 2015;56:287

Steroid Therapy in ARDS
Summary

- Corticosteroid treatment should be considered in the management of ARDS
  - As early (< 72 h) as possible, or within 7 ~ 14 days
  - Low-dose steroid therapy
  - Prolonged course
- SMC protocol: early, low-dose, prolonged treatment
  - Within 72 h (~ 7 days) after diagnosis of ARDS
  - 1mg/kg loading and 1mg/kg/day over 24 h (CIV)
  - Assessment of responsiveness to steroid therapy at 7 days: lung injury score
    - Response (+): sustained steroid treatment for 14 days and tapered (28 days)
    - Response (−): tapered within 7 days (14 days)