STEROID IN ARDS

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QUESTION 1

Steroids beneficial or not ?

QUESTION 2

Early or Late ARDS?
Subpopulation?

QUESTION 3

Type of steroid & dosing regimens

HISTORICAL PERSPECTIVE

Timeline:

Early theoretical use (1970-1980s)- hypothesis – steroids could suppress excessive inflammation – use controversial due to limited evidence

Initial Negative trials -1987 (Bernard et al.) small RCT in early ARDS – no survival benefit with raised concerns of infection

Revival for LATE phase ARDS- 1998 (Meduri et al.,)

Prolonged low dose MPS – reduced duration of mechanical ventilation

Renewed interest in steroids

ARDSNet Trial, NEJM- 2006

Low dose MPS in **early ARDS**(within 72hrs of onset) No mortality benefit, higher risk of neuromuscular weakness and infections.

Timeline

Shift towards evidence based use (2010s)
Trials focused on refining timing, dosing and patient selection

Breakthrough with DEXA ARDS (2020)
-

- **Dexamethasone** significantly reduced mortality and increased ventilator-free days in moderate-to-severe ARDS

Steroids in COVID 19 ARDS (2020-2021) (RECOVERY trial 2020) Dexamethasone reduced mortality in patients with severe COVID-19, reinforcing the findings of DEXA-ARDS

2024 focused update SCCM:

Conditional recommendation- suggest corticosteroids in moderate to severe ARDS

INTRODUCTION

Berlin Definition	Rationale for Updating Criteria
Acute onset within 1 week of known insult or new or worsening respiratory symptoms	Onset may be more indolent for some insults, such as COVID-19
Bilateral opacities on chest radiography or computed tomography not fully explained by effusions, lobar/lung collapse, or nodules	Chest radiography and computed tomography not available in some clinical settings
Three severity categories defined by PaO_2:FiO_2	Pulse oximetric measurement of SpO_2:FiO_2 is widely used and validated as a surrogate for PaO_2:FiO_2
Requirement for invasive or noninvasive mechanical ventilation such that PEEP ≥ 5 cm H_2O is required for all categories of oxygenation severity except mild, which can also be met with CPAP ≥ 5 cm H_2O	HFNO increasingly being used in patients with severe hypoxemia who otherwise meet ARDS criteria
	Invasive and noninvasive mechanical ventilation not available in resource-limited settings

A New Global Definition of Acute Respiratory Distress Syndrome, Am J Respir Crit Care Med, Vol 209, Iss 1, pp 37–47, Jan 1, 2024.

PATHOPHYSIOLOGY

ROLE OF INFLAMMATION IN ARDS PROGRESSION

- Early ARDS is characterized by **diffuse alveolar damage**, driven by pro-inflammatory mediators like **TNF-α** and **IL-1, IL-6, IL-8**
- Pro-inflammatory cytokines recruit and activate PMNs, release toxic mediators such as reactive oxygen species (ROS) and proteases.
- Disruption of alveolar epithelium and basal membranes.→ Impaired fluid resorption → protein and blood cell accumulation in alveolar spaces.
- Consequences : Surfactant inactivation → Alveolar collapse (atelectasis) →reduced aerated lung volume → Intrapulmonary shunting →Refractory hypoxemia.

Martin, T. R. (1999). Lung Cytokines and ARDS: CHEST
Yang et al. (2021). Understanding the role of neutrophils in acute respiratory distress syndrome. Biomed. J

RATIONALE FOR STEROIDS

•**Controversy**: Efficacy debated for decades.

•**Glucocorticoids Mechanism**: Corticosteroids, potent anti-inflammatory agents bind to cytoplasmic glucocorticoid receptors, regulate transcription of GRE like NF-κβ and reduce expressions of pro inflammatory cytokines

•**Animal Models**: Decreased expression of pro-inflammatory mediators (e.g., TNF-α, IL-1α, IL-1β). and reduce injury through reduction of oxygen radicals from neutrophils.

Phases of Administration of steroids:

•**Early ARDS**: Major alveolar inflammation. Thus, theoretically expected to be relevant treatment for ARDS.

•**Late ARDS**: ongoing inflammation with fibroproliferation, presence of hyaline membranes, and persistent diffuse alveolar damage leading to prolonged mechanical ventilation.

Hong et al. (2022). BMC Pulm. Med.
Kuperminc E, et al. Corticosteroids in ARDS. Journal of Clinical Medicine. 2023

REVIEW OF KEY TRIALS EARLY / LATE ARDS

Patient selection (timing / severity of ARDS)

Dosing regimens (low dose vs high doses)

Duration and tapering of steroids – monitoring

LUNG INJURY SCORE

Parameter	Score 0	Score 1	Score 2	Score 3	Score 4
PaO_2/FiO_2 (mmHg)	≥300	225-299	175-224	100-174	<100
PEEP (cm H_2O)	≤5	6-8	9-11	12-14	≥15
Compliance (ml/cm H_2O)	≥80	60-79	40-59	20-39	≤19
CXR Alveolar Consolidation	0	1	2	3	4

Score Range	**Severity**
0 - 1	Mild
1 - 2.5	Moderate
2.5 ≥	Severe

Murray JF, et al. *Am Rev Respir Dis*. 1988

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**

- Participants: moderate to severe ARDS (PF ratio ≤ 200mmhg with PEEP of ≥10 cmh20 and Fio2 0.5 **≥ at 24h after onset of ARDS**), not having concomitant illness requiring steroids
- Study period :1006 patient screened 2013- 2018 , 277 patient enrolled
- Intervention : Dexamethasone 20mg from days 1-5, 10mg from days 6-10
- Primary Outcome : no. of ventilator – free days at 28 days
- Secondary Outcome : all cause mortality at 60 days

Villaret al. Lancet RespFeb 2020

BASELINE CHARACTERISITICS

	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)
Tidal volume, mL per predicted bodyweight	6·9 (0·7)	6·9 (0·8)
Respiratory rate, breaths per min	23 (5)	23 (5)
FiO_2	0·64 (0·16)	0·64 (0·15)
Positive end-expiratory pressure, cm H_2O	12·6 (2·7)	12·5 (2·6)
Inspiratory plateau pressure, cm H_2O†	26·4 (4·1)	26·1 (4·2)
$PaCO_2$, mm Hg	47·9 (10·2)	47·8 (9·3)
Arterial pH	7·34 (0·09)	7·35 (0·08)

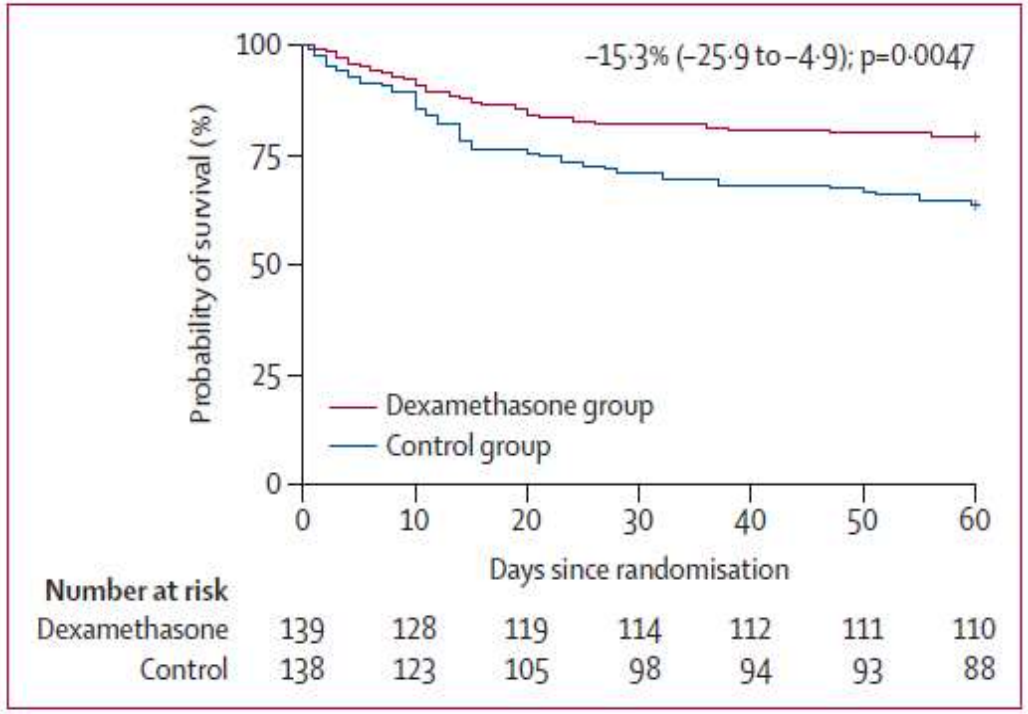
Villaret al. Lancet RespFeb 2020

Table 2: Outcomes , adverse events and complications:

	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

Data are n (%) or mean (SD). ICU=intensive care unit. *Data included the period from randomisation to day 10 (for hyperglycaemia) and from randomisation to ICU discharge (for new infections and barotrauma).

Figure 1: Kaplan – Meier survival estimated during the first 60 days of trail



Villaret al. Lancet RespFeb 2020

- Largest RCT on corticosteroids in moderate-to-severe ARDS using lung-protective ventilation (277 patients across 17 ICUs).
- Patients reassessed after 24 hours of ICU care to confirm ARDS diagnosis
- Early Dexamethasone Administration: Reduced ventilator duration and hospital mortality.
- Observed treatment effect was larger than expected
- Biomarkers of inflammation before and after treatment was not measured
- Did not achieve the target sample size as the study was terminated early.(Slow recruitment)

Methylprednisolone Infusion in Early Severe ARDS*

Results of a Randomized Controlled Trial

- RCT , double blind conducted in MICU in 5 medical centres
- Participants: 500 patients screened from 1997 to 2002, 99 patients with severe ARDS (PF ratio ≤ 200 , Duration ≤ 72hrs of onset , Predominant
- Intervention : MPS 1mg/kg/day loading dose,1 mg/kg/d from day 1 to day 14, 0.5 mg/kg/d from day 15 to 21, 0.25 mg/kg/d from day 22 to 25, and 0.125 mg/kg/d from day 26 to 28 at 6 hrly interval
- Primary Outcome : 1 point reduction in lung injury score or successful extubation by day 7
- Secondary Outcome : Improvement in MODS and development of nosocomial infections.

Meduri GU, et al. *Chest*. 2007;131(4):954-963

BASELINE CHARACTERISTICS

Characteristics	Methylprednisolone (n = 63)	Placebo (n = 28)	p Value (n = 91)
Age, yr	50.1 ± 15.3	53.2 ± 15.3	0.38
Male gender	34 (54.0)	13 (46.4)	0.51
White ethnic group†	37 (58.7)	20 (71.4)	0.25
APACHE III score at ICU entry‡	60.2 ± 20.2	57.9 ± 21.0	0.63
Conditions precipitating ARDS§			
Pneumonia	26 (41.3)	12 (42.9)	0.89
Aspiration of gastric content	13 (20.6)	5 (17.9)	0.76
Sepsis (extrapulmonary)	8 (12.7)	7 (25.0)	0.22
Other	16 (25.4)	4 (14.3)	0.24
Direct cause of ARDS	44 (71.0)	16 (59.3)	0.28
Sepsis-induced ARDS	42 (66.7)	19 (67.8)	0.91
Bacteremia	14 (22.2)	6 (21)	0.93
Catecholamine-dependent shock	15 (23.8)	13 (46.4)	0.03
Postsurgical ARDS	22 (34.9)	12 (42.9)	0.47
LIS‖	3.21 ± 0.41	3.11 ± 0.41	0.27
PEEP, cm H_2O	13 ± 5.0	11.2 ± 4.0	0.08
PaO_2/FIO_2 ratio	118.4 ± 51.2	125.9 ± 38.6	0.44
MODS score‖¶	2.1 ± 0.8	2.2 ± 1.1	0.54
C-reactive protein level, mg/dL	25.0 ± 8.8	26.4 ± 10.1	0.55
Baseline cortisol level, μg/dL	21.9 ± 1.8	25.9 ± 1.8	0.21
Adrenal insufficiency‖	16 (25.4)	7 (25.0)	0.88
Persistent ARDS at 24 h#	44 (77.2)	21 (84)	0.49

Meduri GU, et al. *Chest*. 2007;131(4):954-963

OUTCOME MEASURES : AT day 7 and ICU mortality

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

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
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

Meduri GU, et al. *Chest*. 2007;131(4):954-963

- Small sample size
- Imbalances among patients with catecholamine-dependent shock would have biased the estimate of the treatment effect on mortality.
- Failure to incorporate weaning procedure
- The patient who failed to improve LIS between study days 7 and 9, the patient left the treatment arm of the study to receive unblinded methylprednisolone therapy (2 mg/kg/d) for unresolving ARDS .

Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial

Surat Tongyoo[1*], Chairat Permpikul[1], Wasineenart Mongkolpun[1], Veerapong Vattanavanit[1,2], Suthipol Udompanturak[1], Mehmet Kocak[3] and G. Umberto Meduri[4]

- RCT , double blind conducted in single centre dec 2009-2014
- Participants: 196 adult patient with severe sepsis within 12h of meeting ARDS (included all severity of ARDS with 55% of moderate ARDS,. Cause of sepsis pneumonia 50%> UTI 18%
- Intervention : Hydrocortisone 50mg every 6 hrs for 7 days
- Primary Outcome : 28 day all cause mortality
- Secondary Outcome : Survival without organ support and 60 day mortality

Tongyoo et al. (2016) Critical Care, 20:329

PRIMARY AND SECONDARY OUTCOME :

	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

By day 28, the treated group had a nonsignificant reduction in duration (days) of MV , vasopressor support, as well as a nonsignificant increase in patients alive on day 28 without organ support

Significant improvement in PF ratio and hydrocortisone group had a significantly lower LIS over course of 7 days and day 14 (p=0.03 and 0.003)
Hyperglycemia was more frequent in the steroid group (80.6% vs. 67.7%, p = 0.04).

Tongyoo et al. (2016) Critical Care, 20:329

Effect of Prolonged Methylprednisolone Therapy in Unresolving Acute Respiratory Distress Syndrome

- RCT , double blind conducted in MICU in 4 medical centres from 1994-1996
- Participants: 24 patients with severe ARDS (LIS of ≥2.5 by **7th day of ARDS)**
- Intervention : MPS 2mg/kg/day loading dose, 2mg/kg/day (day 1 to 14)→ 1mg/kg/day (day 15 to 21)→0.5mg/kg/day (day 22 to 28)→0.25mg/kg/day on day 29 and 30 and 0.125mg/kg/day on 31 and 32 at 6 hrly interval
- Primary Outcome : Improvement in lung function (assessed by LIS score)
- Secondary Outcome : Improvement in MODS and development of nosocomial infections.

Meduri, G. U., et al. (1998). JAMA

OUTCOME MEASURES ON STUDY DAY 10

Outcome Measures	Methylprednisolone	Placebo	*P* Value
No. of patients	16	8	NA
Ratio of Pao_2 to FIo_2	262 (19)	148 (35)	<.001
Lung injury score	1.7 (0.1)	3.0 (0.2)	<.001
Patients with >1-point reduction in LIS, No. (%)	16 (100)	2 (25)	<.001
Crossed over because of failure to improve LIS†	0	4	.007
Pulmonary artery pressure‡	22.5 (3.2)	30 (2.7)	.01
Successful extubation, No. (%)	7 (44)	0 (0)	.05
MODS score	0.7 (0.2)§	1.8 (0.3)	<.001
Infections per 100 patient-days of treatment‖	8	7	.99
New ventilator-associated pneumonia	6	1	.70
Survivors, No. (%)	16 (100)	6 (75)	.10

Outcome Measures	Methylprednisolone	Placebo	*P* Value
Survivors of ICU admission, No. (%)	16 (100)	3 (37)	.002
Survivors of hospital admission, No. (%)	14 (87)	3 (37)	.03
Death associated with unresolving ARDS, No.†	0 of 2	5 of 5	NA
MODS-free days by study day 28, mean (SEM)‡	16 (2)	6 (2)	.005
Duration of mechanical ventilation, median, d	11.5	23	.001

Prolonged administration of MPS with unresolving ARDS was associated with improvement in lung injury and MODS score

Meduri, G. U., et al. (1998). JAMA

COMPLICATIONS OBSERVED DURING THERAPY

Complications	Methylprednisolone*	Placebo
No. of patients	16	8
Patients with a new infection	12 (75)	6 (75)
New infections†	24	10
Pneumonia‡	9 (38)	1 (10)
Sinusitis§	2 (8)	0 (0)
Catheter-related infection	3 (12)	3 (30)
Urinary tract infection	4 (17)	0 (0)
Bacteremia	2 (8)	4 (40)
Candidemia	2 (8)	0 (0)
Others‖	2 (8)	2 (20)
New pneumothorax	2 (12)	4 (50)
Reduction in hemoglobin >0.20	1 (6)	4 (50)
New hyperglycemia (glucose >13.9 mmol/L [250 mg/dL])	5 (31)	4 (50)

There was no statistically significant difference in any variable among the 2 groups

Meduri, G. U., et al. (1998). Critical Care Medicine.

Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

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

STUDY DESIGN	1997 - 2003 RCT Multicentre
PARTICIPANTS	• **7-28 days after onset of ARDS** with PF ratio ≤ 200 • Intubated, MV
INTERVENTION	2 mg/kg of MPS → 0.5 mg/kg every 6 hrs (2mg) for 14 days→ 0.5 mg /kg every 12 hours (1mg) for 7 days, and then tapering of the dose
PRIMARY AND SECONDARY OUTCOME	• The primary end point was mortality at 60 days. • Secondary end points included the number of ventilator-free days and organ-failure–free days at 28, infectious complications

Steinberg et al., N Engl J Med. 2006

PRIMARY AND SECONDARY OUTCOMES AND ADVERSE EVENTS

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	
60-Day mortality according to baseline BAL procollagen peptide type III level			
< Median (%)	9	35	0.03
No. of patients	23	23	
> Median (%)†	19	4	0.10
No. of patients	21	24	

- The 60- day hospital mortality rate was 28.6 % in the placebo group (95 % CI, 20.3 - 38.6 %) and 29.2 % in MPS group (95 % CI, 20.8 to 39.4%; P = 1.0);
- Rates were 35% vs 8% (P = 0.02) , more in ARDS > 14 days of onset in steroid group
- Steroids increased ventilator-free days and ICU-free days (early benefits)

Steinberg et al., N Engl J Med. 2006

POST HOC ANALYSES OF OUTCOMES AND ADVERSE EVENTS AT 180 DAYS.

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
180-Day mortality — %	31.9	31.5	1.0
95% CI	23.2–42.0	22.8–41.7	
No. of ventilator-free days at day 180			0.04
Median	149	159	
Interquartile range	0–167	13–173	
No. of ICU-free days at day 180			0.27
Median	150	152	
Interquartile range	0–164	13–168	
Survivors			0.006
Days of assisted ventilation up to 180 days			
Median	18	11	
Interquartile range	10–33	6–22	
Days of ICU stay up to 180 days			0.29
Median	20	17	
Interquartile range	11–31	10–31	
Days of hospitalization up to 180 days			0.73
Median	29	26	
Interquartile range	19–40	19–43	
Neuromyopathy — no./ total no. (%)			0.18
Retrospective review	10/43 (23)	15/44 (34)	
Prospective review	11/48 (23)	11/44 (25)	0.67
Overall	21/91 (22)	26/88 (30)	0.20
180-Day mortality according to time from ARDS onset			
7–13 Days — %	39	27	0.14
No. of patients	66	66	
>14 Days — %†	12	44	0.01
No. of patients	25	23	

- At 180 days, the rates were 31.9%and 31.5 % (P = 1.0) , more in ARDS > 14 days of onset in steroid group

Conclusion:

- Early steroids (before Day 14) may help in reducing ventilator duration but no difference in mortality
- Steroids should be avoided in late ARDS (> Day 14) due to potential harm

Steinberg et al., N Engl J Med. 2006

Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome*

Djillali Annane, MD, PhD; Véronique Sébille, PhD; Eric Bellissant, MD, PhD; for the Ger-Inf-05 Study Group

- Retrospective analysis of RCT,conducted in 19 ICU units in France.
- Participants: 300 patients, 177 ARDS: 129 non responder , 48 responder
- Intervention : 50 mg of hydrocortisone every 6 hrs and 50 mcg of oral fludrocortisone once a day- 7 days
- Primary Outcome : 28-day survival distribution in non responders.
- Secondary Outcome : a) 28-day survival distributions in responders;

  b) ICU mortality rates and Hospital discharge rates at day28

  c) No. of days alive and off the ventilator until day 28

Annane D, et al. Critical Care Medicine. 2006

Frequency of fatal events in 177 septic shock patients with early ARDS, according to the response to a short corticotropin test

	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

Annane D, et al. Critical Care Medicine. 2006

Frequency of fatal events in 120 septic shock patients without ARDS, according to the response to a short corticotropin test

	Nonresponders			Responders			All Patients		
	Placebo (n = 47)	Steroids (n = 52)	*p*	Placebo (n = 9)	Steroids (n = 12)	*p*	Placebo (n = 56)	Steroids (n = 64)	*p*
Day 28 mortality	23 (49)	27 (52)		6 (67)	5 (42)		29 (52)	32 (50)	
Unadjusted hazard ratio	[a]		.777[b]	[a]		.256[b]	[a]		.819[b]
Adjusted hazard ratio	[a]		[a]	[a]		[a]	[a]		[a]
Relative risk	1.06 (0.72–1.57)		.767	0.63 (0.28–1.41)		.387	0.97 (0.68–1.37)		.845
Adjusted odds ratio	0.90 (0.37–2.17)		.813	0.50 (0.01–8.42)		.968	0.73 (0.33–1.63)		.446
ICU mortality	28 (60)	30 (58)		6 (67)	6 (50)		34 (61)	36 (56)	
Relative risk	0.97 (0.70–1.35)		.849	0.75 (0.36–1.57)		.661	0.93 (0.69–1.25)		.621
Adjusted odds ratio	0.73 (0.30–1.80)		.499	0.80 (0.01–13.28)		1.000	0.69 (0.31–1.57)		.378
Hospital mortality	30 (64)	33 (63)		6 (67)	7 (58)		36 (64)	40 (63)	
Relative risk	0.99 (0.74–1.34)		.970	0.87 (0.45–1.70)		1.000	0.97 (0.74–1.28)		.840
Adjusted odds ratio	0.75 (0.30–1.89)		.542	0.80 (0.03–14.89)		.858	0.75 (0.33–1.71)		.489

Conclusion : 7 day treatment with low doses of corticosteroid was associated with better outcomes in septic shock with early acute ARDS non responders

ne D, et al. Critical Care Medicine. 2006

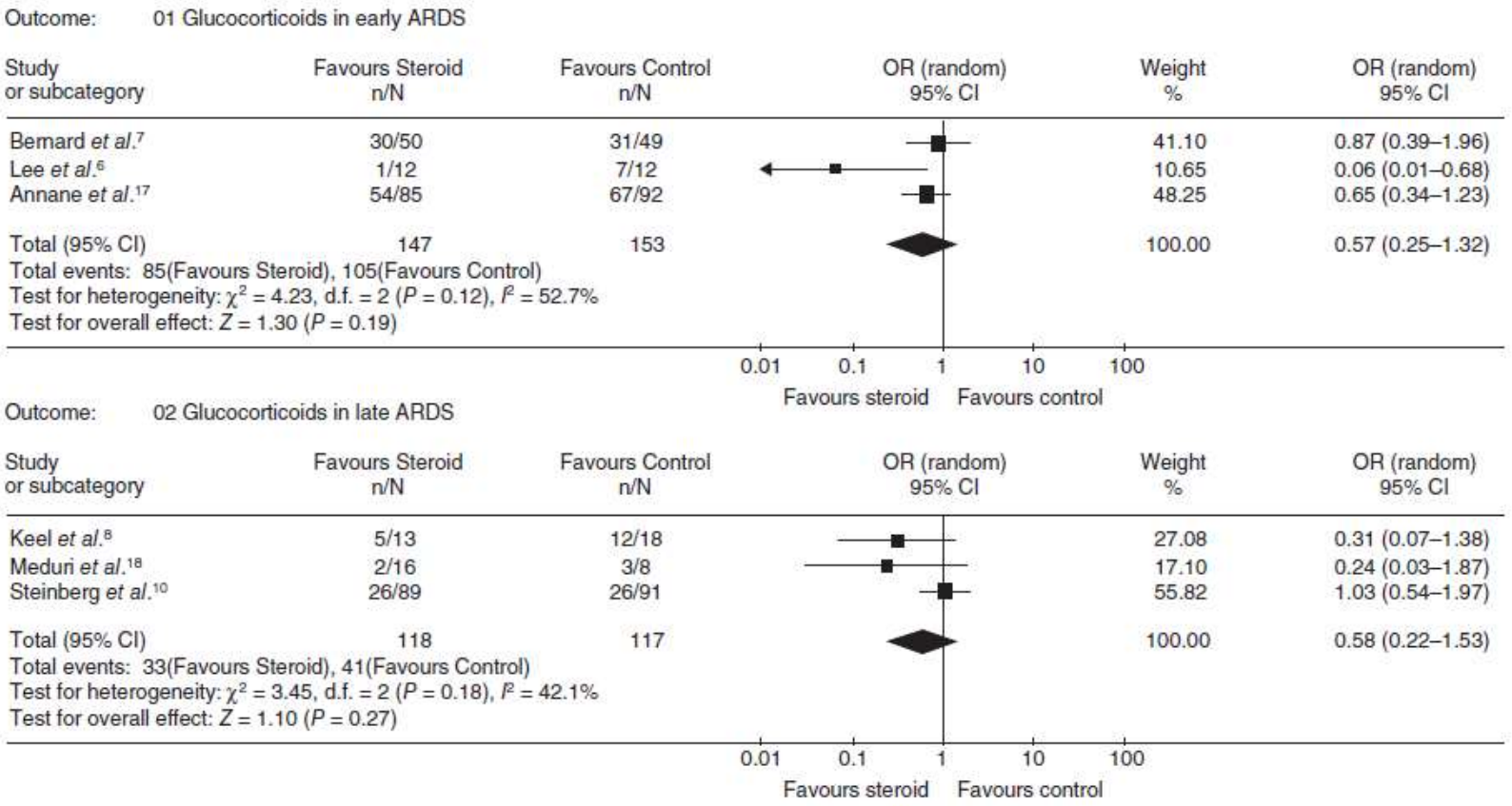
SHIFT IN RESEARCH OVER TIME

EARLY VS LATE ARDS?

Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis

RITESH AGARWAL, ALOK NATH, ASHUTOSH N. AGGARWAL AND DHEERAJ GUPTA

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh, India



Glucocorticoids do not decrease the mortality in patients with early and late ARDS

AGARWAL R. et al. (2007). Respirology, 12(4), 585–590

REVIEW Open Access

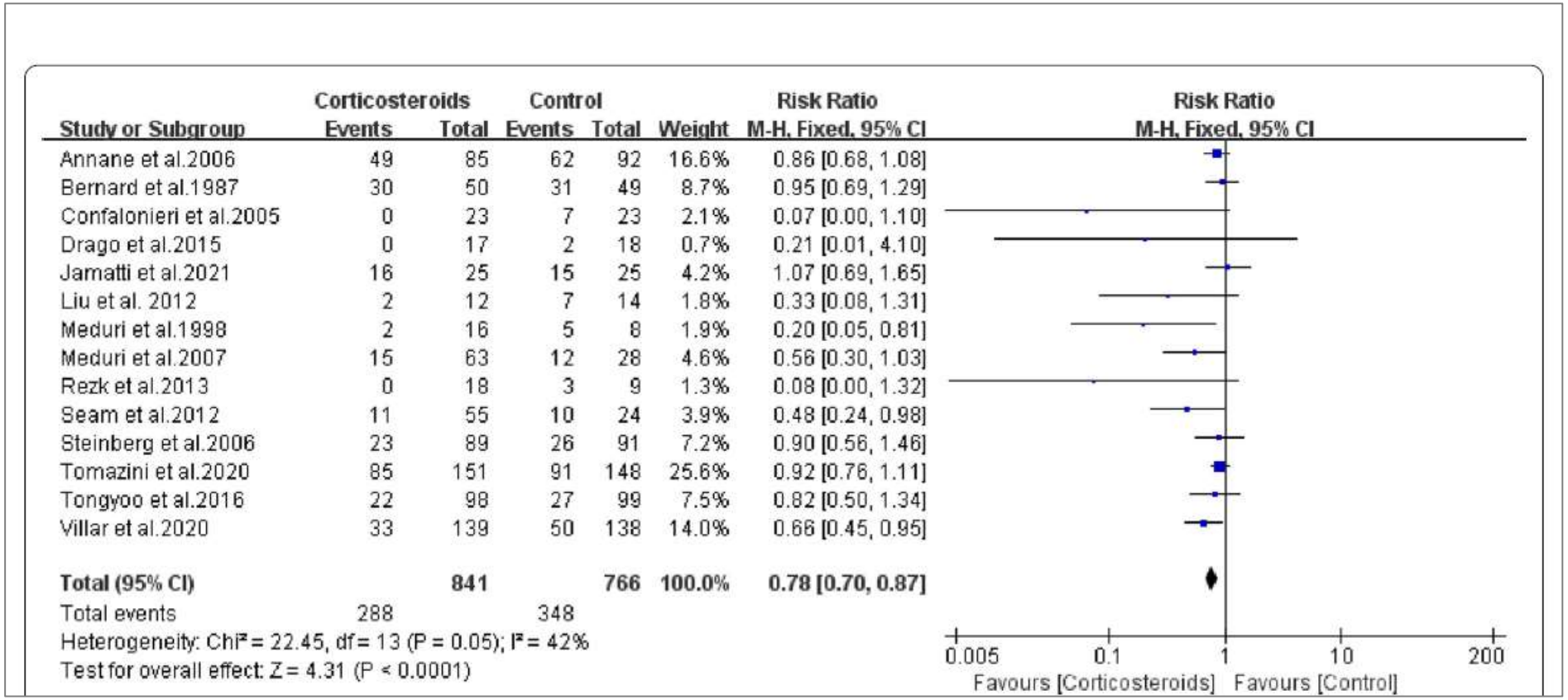
Safety and efficacy of corticosteroids in ARDS patients: a systematic review and meta-analysis of RCT data

Xinyan Chang[1,3], Shaojun Li[2,3], Yueqiang Fu[1,3], Hongxing Dang[1,3] and Chengjun Liu[1,3*]

- 14 RCTs (n = 1607) included, evaluating corticosteroids safety & efficacy in ARDS
- The primary outcome was 28-day mortality
- Subgroup analysis: Adults vs Paediatrics and duration of treatment
- Unanswered questions: Optimal dose, best steroid choice

Chang X, et al. a systematic review and meta-analysis of RCT data. Respiratory Research. 2022

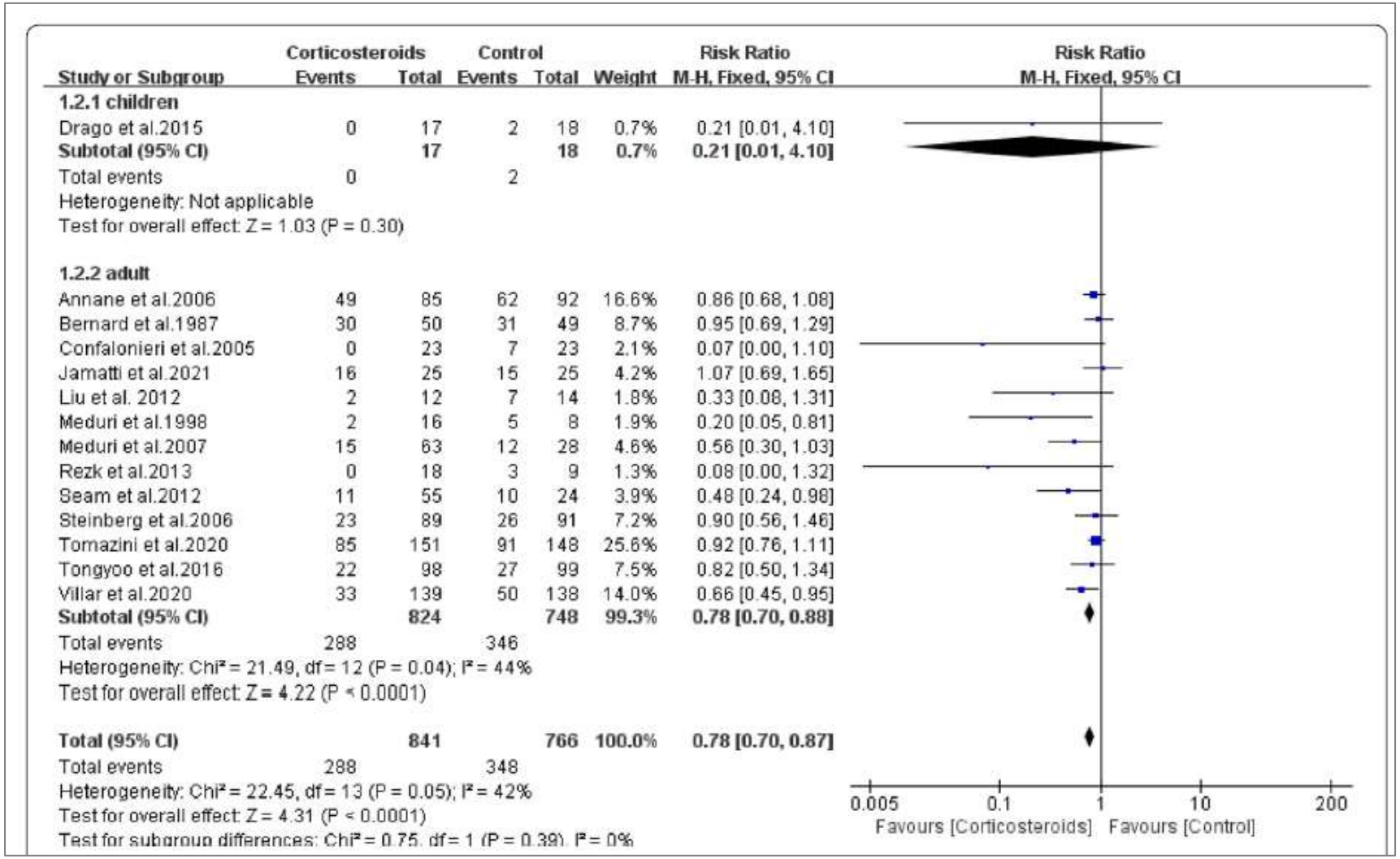
The effect of corticosteroids on Mortality at 28 days among patients with ARDS



Corticosteroids reduced 28-day mortality (RR = 0.78, 95% CI: 0.70–0.87, p < 0.01)

Chang X, et al. a systematic review and meta-analysis of RCT data. Respiratory Research. 2022

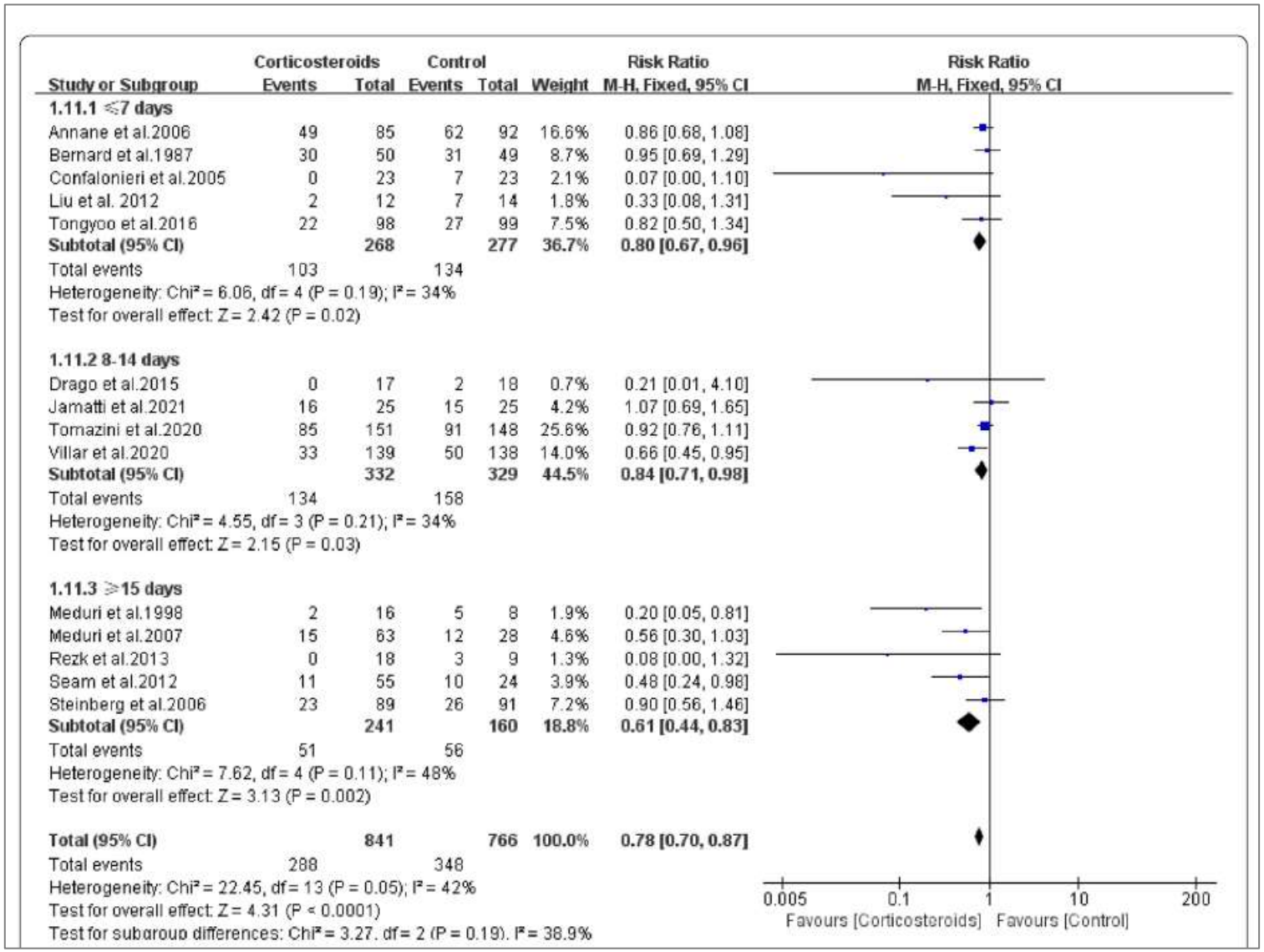
The effect of corticosteroids on Mortality at 28 days. Studies subdivided by adults and children



Subgroup analyses revealed that the mortality reduction was significant among adults (RR = 0.78; 95% CI: 0.70–0.88; P < 0.01)

Chang X, et al. a systematic review and meta-analysis of RCT data. Respiratory Research. 2022

The effect of corticosteroids on mortality at 28 days. Studies subdivided by treatment duration of corticosteroids



- Longer duration (>15 days) is associated with the most significant survival benefit.
- Short-term use (≤7 days) shows only a modest reduction in mortality.
- Consistency across studies supports the effectiveness of prolonged corticosteroid therapy in ARDS.

Chang X, et al. a systematic review and meta-analysis of RCT data. Respiratory Research. 2022

RESEARCH Open Access

Use of glucocorticoids in patients with acute respiratory distress syndrome: a meta-analysis and trial sequential analysis

Yazan Zayed[1*], Mahmoud Barbarawi[1], Esraa Ismail[2], Varun Samji[1], Josiane Kerbage[3], Fatima Rizk[4], Mohammad Salih[1], Areeg Bala[1], Michele Obeid[1], Smit Deliwala[1], Sherry Demian[1], Ibrahim Al-Sanouri[5] and Raju Reddy[6]

- Meta-analysis of 8 RCTs (n = 1091)
- Participants : ARDS according to Berlin definition were included, studies examining prophylactic effects of steroids at high risk of ARDS were excluded
- Our primary outcome was hospital mortality.
- Secondary outcomes included ICU mortality, number of ventilator-free days at day 28, incidence of nosocomial infections, and hyperglycemia.

Zayed et al. (2020). a meta-analysis and trial sequential analysis. Journal of Intensive Care

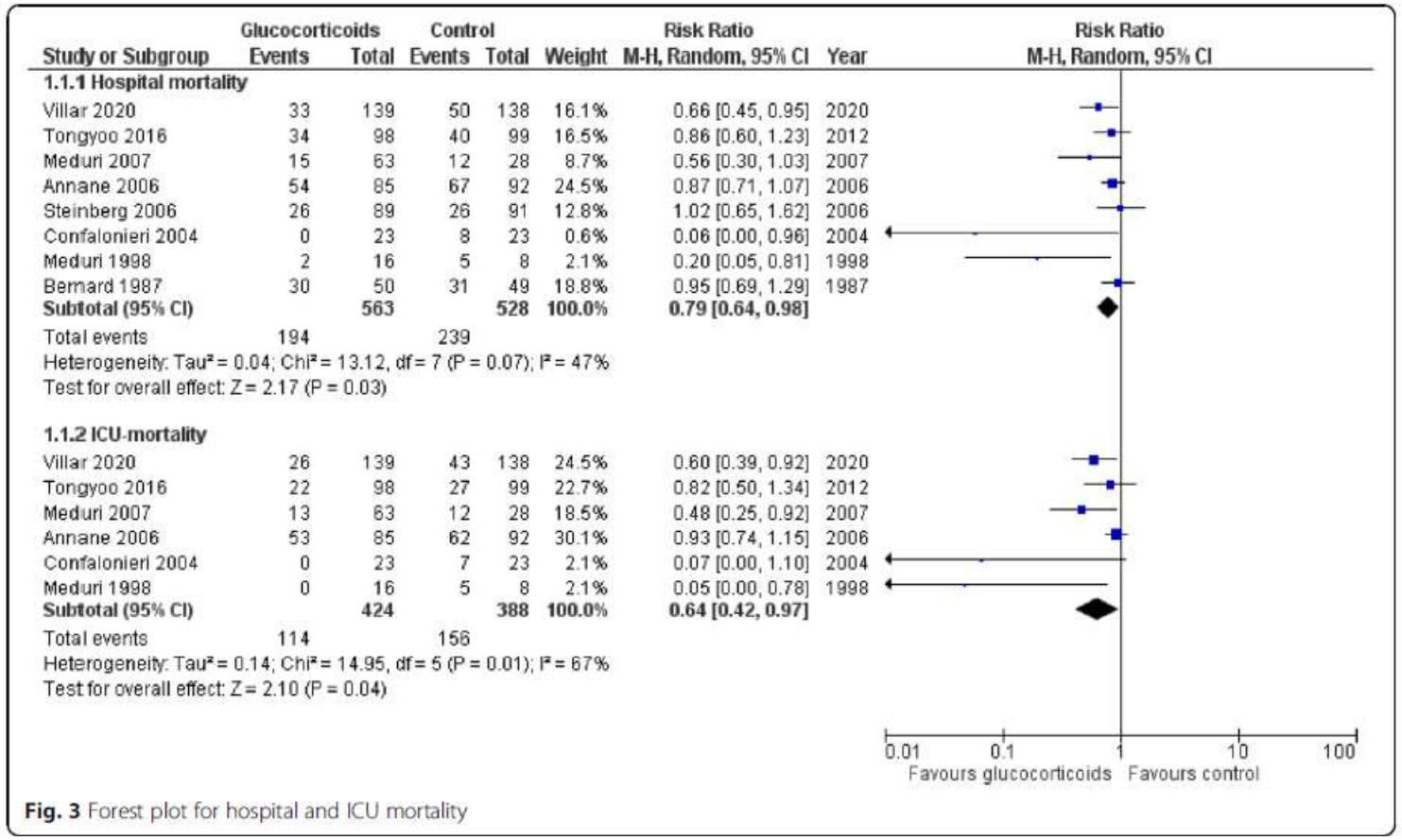


Fig. 3 Forest plot for hospital and ICU mortality

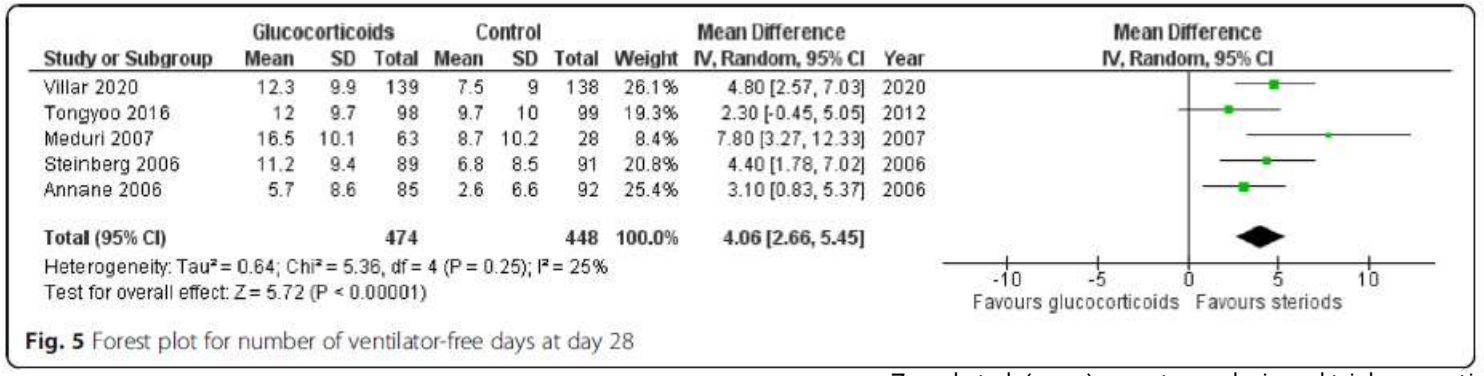


Fig. 5 Forest plot for number of ventilator-free days at day 28

Glucocorticoid use significantly reduced hospital mortality (RR = 0.79, 95% CI: 0.64–0.98, p = 0.03).
ICU mortality was also lower with steroids (RR = 0.64, 95% CI: 0.42–0.97, p = 0.04).
Patients receiving steroids had 4.06 more ventilator-free days at day 28 (p < 0.001).

Zayed et al. (2020). a meta-analysis and trial sequential analysis. Journal of Intensive Care

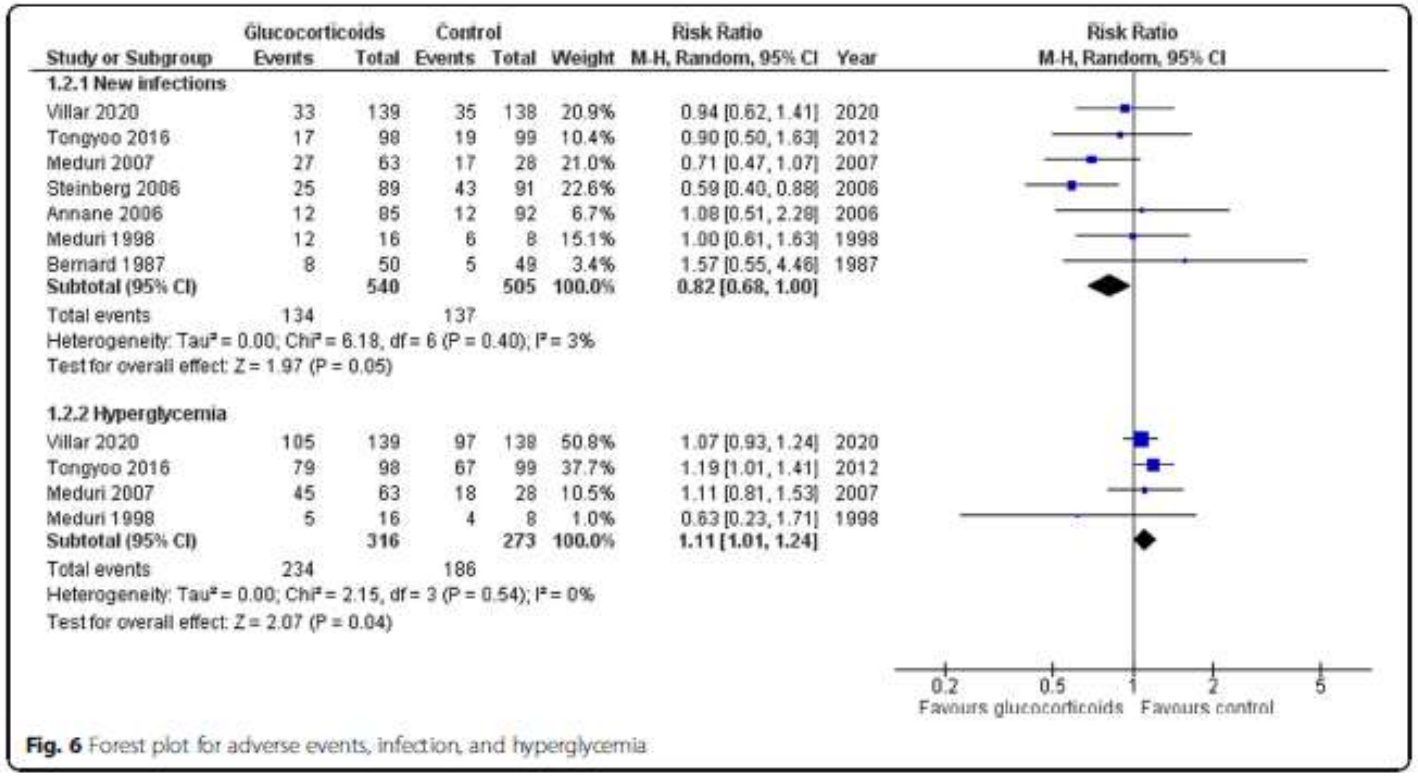


Fig. 6 Forest plot for adverse events, infection, and hyperglycemia

No significant increase in nosocomial infections (RR = 0.82, p = 0.05). Hyperglycemia risk was higher in the steroid group (RR = 1.11, p = 0.04).

Zayed et al. (2020). a meta-analysis and trial sequential analysis. Journal of Intensive Care

- Use of glucocorticoids is associated with significant reduction in mortality and duration of mechanical ventilation without an increased risk of infection but with an increased incidence of hyperglycemia.
- This study included RCTs that investigated different types and dosages of glucocorticoids with various durations.
- The patient-level data analysis based on the severity and underlying etiology of ARDS were lacking .
- Trail sequence analysis revealed evidence is insufficient

COVID VS NON COVID?

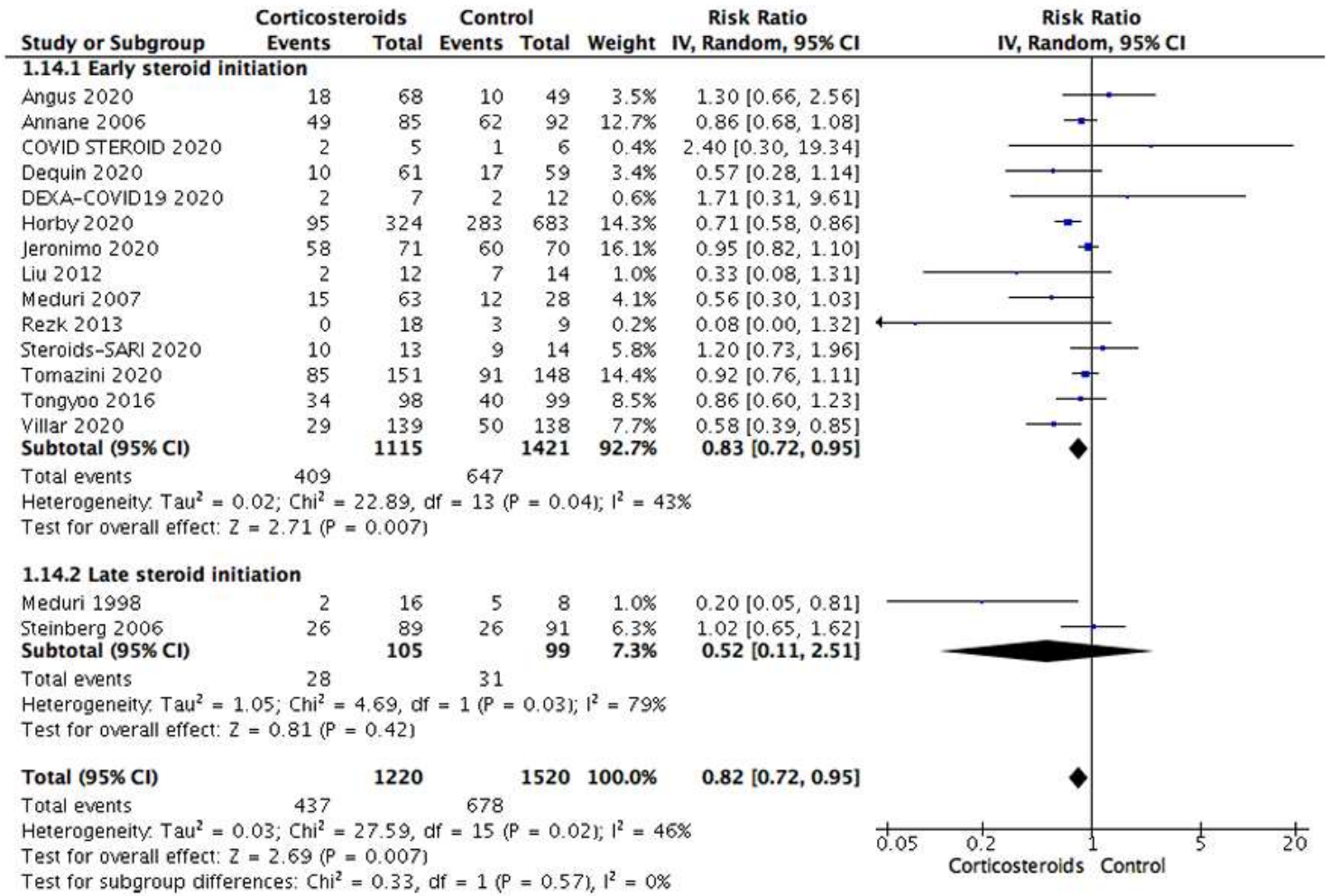
Study	Population with Sample Size	Inclusion Criteria	Exclusion Criteria	Intervention	Comparison	Result and Outcome
RECOVERY[1] (2020)	COVID-19 patients hospitalized with hypoxemia and respiratory failure N=6425 Dexa- 2104	Adults hospitalized with confirmed COVID-19 Stratification : need for oxygen therapy	Pregnant women, patients already on mechanical ventilation	Dexamethasone (6 mg/day for 10 days)	Usual care	• Reduced mortality (22.9% vs. 25.7%) in patients requiring oxygen support • . No significant effect in those not requiring oxygen • Incidence of death lower in DEXA group receiving MV
CODEX[2] (2020)	COVID-19 patients with moderate-to-severe ARDS N=299	Adults with confirmed COVID-19, moderate-to-severe ARDS, and on supplemental oxygen	Pregnant women, patients with active tuberculosis or systemic fungal infections, and those with other contraindications to corticosteroids	Dexamethasone (20 mg/day – 5 days 10mg /day - 10 days)	Placebo	• Mean ventilator free days 6.6 vs 4 days at 28days • No difference in all cause mortality , mechanical ventilation duration • 31% needed insulin for glycemic control
REMAP-CAP COVID[3] (2020)	critically ill COVID-19 patients with ARDS N=614	Critically ill adult patients with confirmed COVID-19, ARDS, and requiring organ support	Patients with contraindications to corticosteroids, pregnant women, or those requiring interventions for severe comorbidities	Hydrocortisone (200 mg/day for up to 7 days)	No steroids (placebo)	• The primary end point- organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days • However, trial terminated early

The RECOVERY Collaborative Group (2020). Dexamethasone in hospitalized patients with Covid-19. NEJM, 384(8), 693-704.[1]
Rodríguez, J. P., et al. (2020). Corticosteroid therapy for COVID-19: Results of the CODEX study. European Respiratory Journal, 56(6)[2]
The REMAP-CAP Investigators (2021). Interleukin-6 receptor antagonists in critically ill patients with COVID-19. NEJM, 384(16), 1491-1502.[3]

STEROID SUBTYPE AND INITIATION

SCCM/ESCIM Meta- analysis of ARDS studies

Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by steroid initiation time. Df = degrees of freedom.

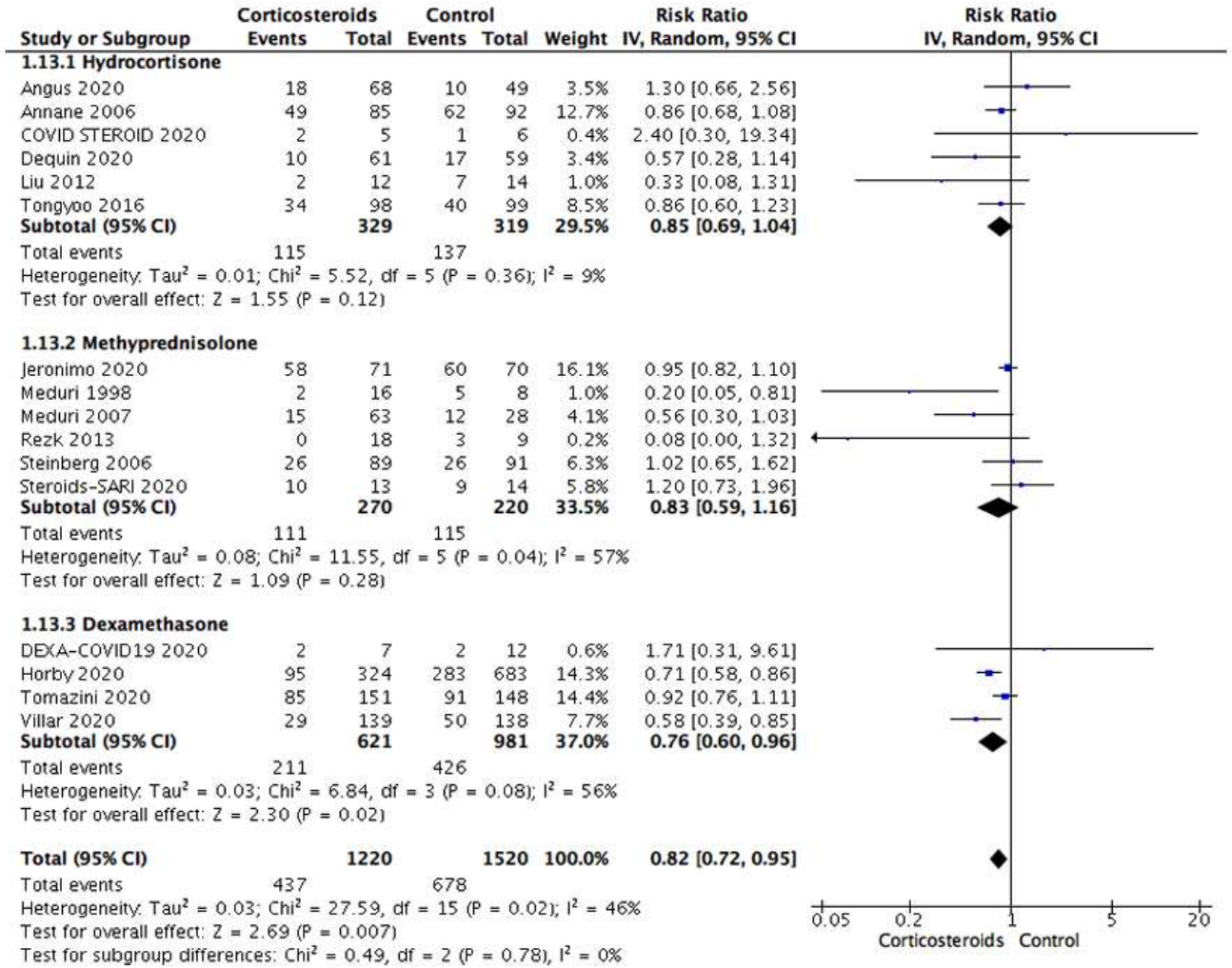


Study favours early steroid initiation

Chaudhuri D, et al. Critical Care Medicine. Online special article. January 19, 2024

SCCM/ESCIM Meta- analysis of ARDS studies

Forest plot: Effect of corticosteroids on mortality. Studies are grouped by steroid subtype. Df = degrees of freedom.



All steroids: 18% lower rate of all cause mortality compared with placebo RR-0.82(95% CI 0.72to 0.95)

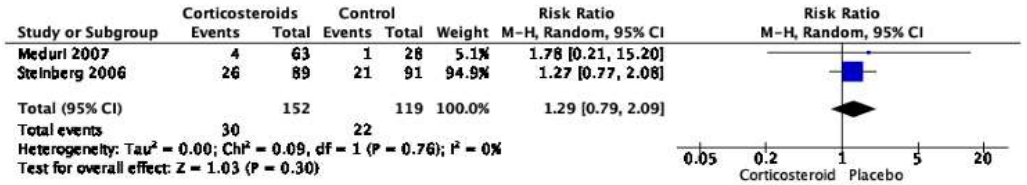
Dexa: 24% lower mortality as compared with placebo

Chaudhuri D, et al. Critical Care Medicine. Online special article. January 19, 2024

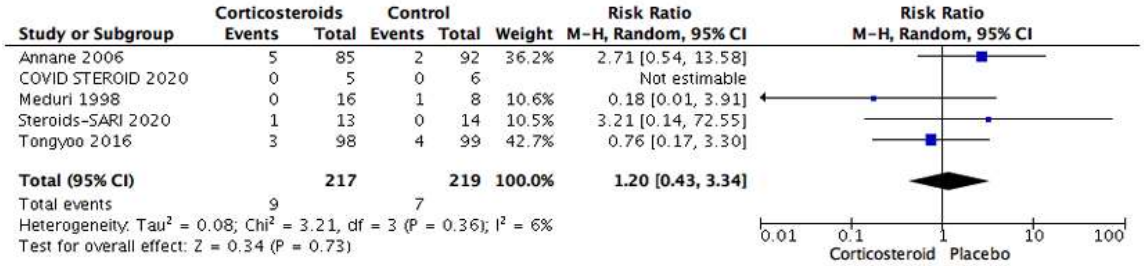
COMPLICATIONS

SCCM/ESCIM Meta- analysis of ARDS studies

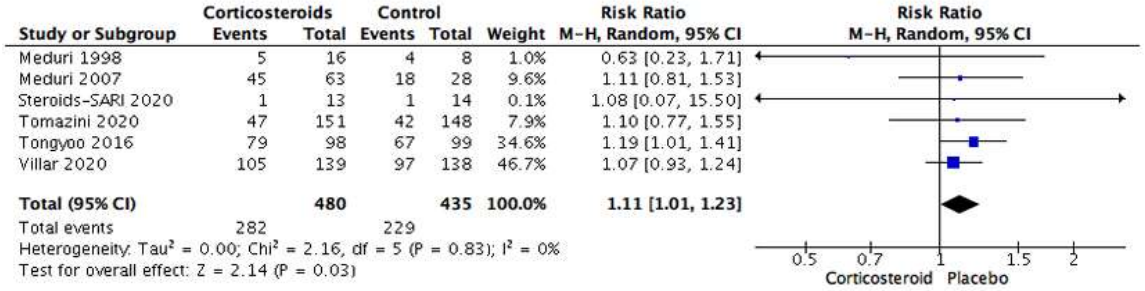
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of neuromuscular weakness. Df = degrees of freedom



Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of gastrointestinal bleeding. Df = degrees of freedom



Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). hyperglycemia. Df = degrees of freedom



There was a significant association between corticosteroid use and a higher incidence of hyperglycemia (OR 1.11, 95% CI [1.01,1.23]).

Chaudhuri D, et al. Critical Care Medicine. Online special article. January 19, 2024

ARDS SECONDARY TO INFLUENZA

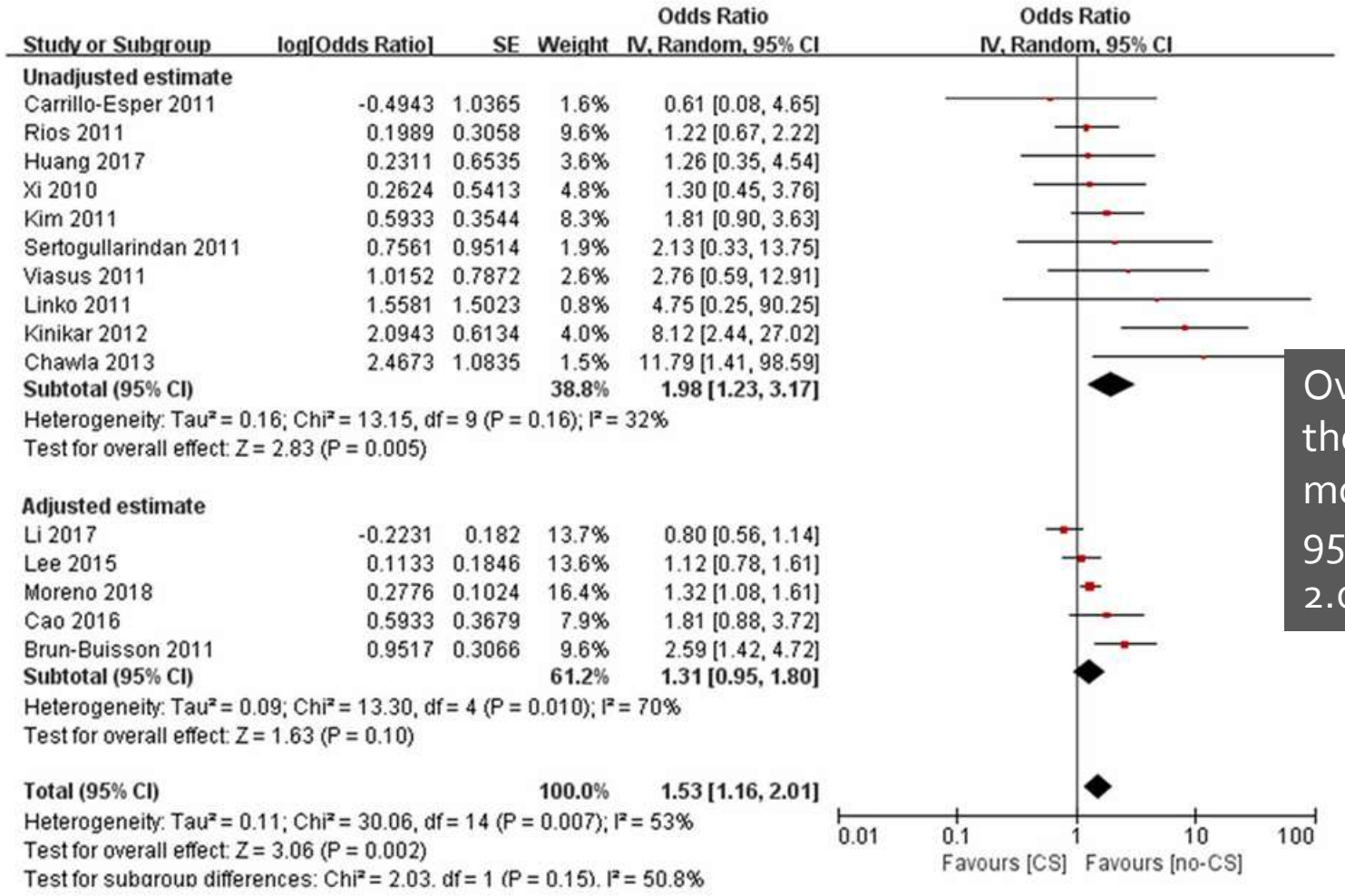
Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis

Yuqing Zhou, Xiaofang Fu, Xiaoxiao Liu, Chenyang Huang, Guo Tian, Cheng Ding, Jie Wu, Lei Lan & Shigui

- Nineteen studies including 6637 individuals were identified, and 18- observational studies and 1- randomized controlled trial (RCT).
- Patients had confirmed influenza-related pneumonia, ARDS (PaO_2/FiO_2 < 300 mmHg)
- MPS (88.7%) commonly used and median duration varied from 5-11 days
- 13 studies included adult patient with A/ H1N1,A/H3N2or B influenza
- Subgroup: Pure ICU patients and mixed patients , corticosteroids were associated with an increased risk of mortality (OR, 1.71 [1.41, 2.06]) and (OR 3.14 [2.58, 3.83] respectively.

Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis

Yuqing Zhou, Xiaofang Fu, Xiaoxiao Liu, Chenyang Huang, Guo Tian, Cheng Ding, Jie Wu, Lei Lan & Shigui



META-ANALYSIS OF STUDIES REPORTING MORTALITY DATA

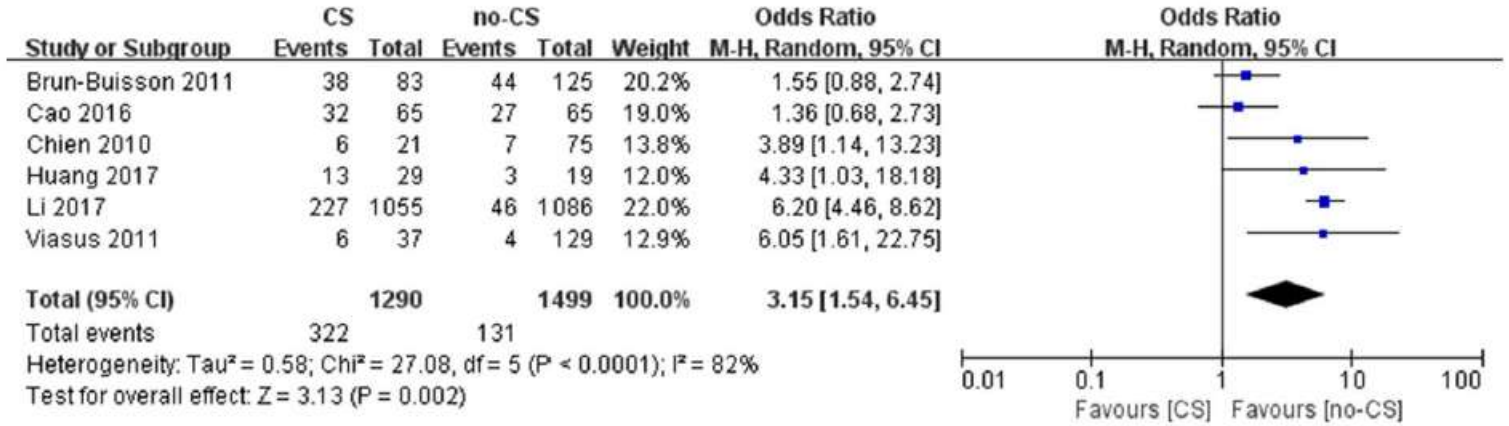
Overall Mortality: Corticosteroid therapy was linked to increase in mortality (Odds Ratio [OR] 1.53, 95% Confidence Interval [CI] [1.16, 2.01]).

Zhou Y, et al: a systematic review and meta-analysis. Scientific Reports. 2020.

Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis

Yuqing Zhou, Xiaofang Fu, Xiaoxiao Liu, Chenyang Huang, Guo Tian, Cheng Ding, Jie Wu, Lei Lan & Shigui

META-ANALYSIS OF STUDIES REPORTING NOSOCOMIAL INFECTION



Study or Subgroup	CS Events	CS Total	no-CS Events	no-CS Total	Weight	Odds Ratio M-H, Random, 95% CI
Brun-Buisson 2011	38	83	44	125	20.2%	1.55 [0.88, 2.74]
Cao 2016	32	65	27	65	19.0%	1.36 [0.68, 2.73]
Chien 2010	6	21	7	75	13.8%	3.89 [1.14, 13.23]
Huang 2017	13	29	3	19	12.0%	4.33 [1.03, 18.18]
Li 2017	227	1055	46	1086	22.0%	6.20 [4.46, 8.62]
Viasus 2011	6	37	4	129	12.9%	6.05 [1.61, 22.75]
Total (95% CI)		**1290**		**1499**	**100.0%**	**3.15 [1.54, 6.45]**
Total events	322		131			

Heterogeneity: Tau² = 0.58; Chi² = 27.08, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 3.13 (P = 0.002)

Figure 4. Meta-analysis of studies reporting nosocomial infection data. CI, confidence interval; OR, odds ratio.

There was a significant association between corticosteroid use and a higher incidence of nosocomial infections (OR 3.15, 95% CI [1.54, 6.45]).

Mc bacteria – Acinetobacter baumannii (35%) , Pseudomonas aeruginosa (13.5%) and stap aureus (49.1%)

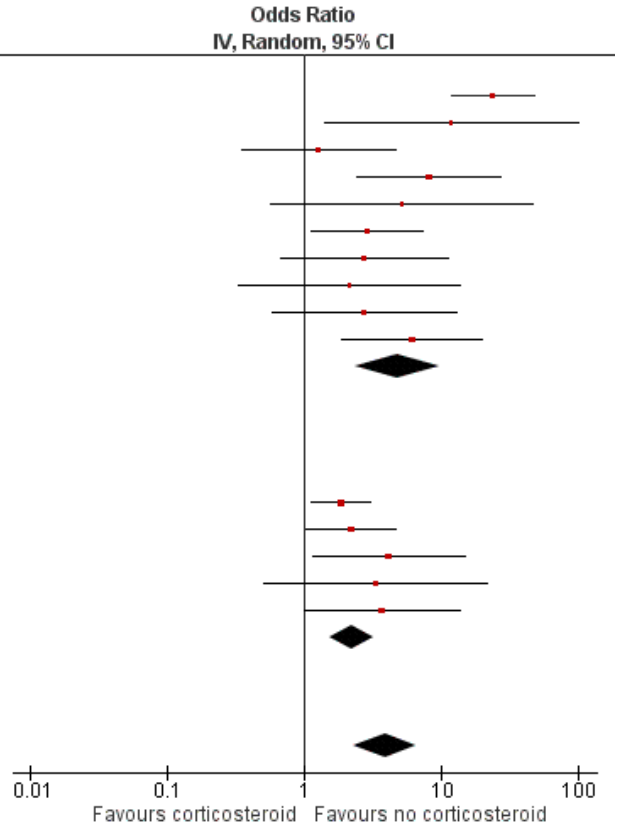
Zhou Y, et al: a systematic review and meta-analysis. Scientific Reports. 2020.

Corticosteroids as adjunctive therapy in the treatment of influenza

Louise Lansbury [1,✉], Chamira Rodrigo [2], Jo Leonardi-Bee [3], Jonathan Nguyen-Van-Tam [4], Wei Shen Lim [2]

Corticosteroid therapy was linked to a significant increase in mortality (Odds Ratio [OR] 3.90, 95% Confidence Interval [CI] [2.31,6.60]).

Study or Subgroup	log[Odds Ratio]	SE	Corticosteroid group Total	No corticosteroid group Total	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Unadjusted mortality						
Balaganesakumar 2013	3.1676	0.3539	70	210	9.4%	23.75 [11.87, 47.52]
Chawla 2013	2.4675	1.0825	38	39	4.0%	11.79 [1.41, 98.41]
Huang 2017	0.2311	0.6577	29	19	6.7%	1.26 [0.35, 4.57]
Kinikar 2012	2.0949	0.6136	21	71	7.1%	8.12 [2.44, 27.05]
Li 2012	1.6376	1.1269	27	19	3.8%	5.14 [0.56, 46.82]
Mady 2012	1.0542	0.4731	43	43	8.3%	2.87 [1.14, 7.25]
Patel 2013	1.0116	0.7124	39	24	6.3%	2.75 [0.68, 11.11]
Sertogullarindan 2011	0.7577	0.9531	7	13	4.6%	2.13 [0.33, 13.81]
Viasus 2011	1.0143	0.7879	37	129	5.7%	2.76 [0.59, 12.92]
Yu 2011a	1.8124	0.6006	54	74	7.2%	6.13 [1.89, 19.88]
Subtotal (95% CI)			**365**	**641**	**62.9%**	**4.79 [2.35, 9.79]**
Heterogeneity: Tau² = 0.81; Chi² = 27.10, df = 9 (P = 0.001); I² = 67%						
Test for overall effect: Z = 4.31 (P < 0.0001)						
1.1.2 Adjusted mortality						
Delaney 2016	0.6152	0.2561	280	327	10.2%	1.85 [1.12, 3.06]
Kim 2011	0.7885	0.3872	107	138	9.1%	2.20 [1.03, 4.70]
Liem 2009	1.4134	0.6543	29	38	6.7%	4.11 [1.14, 14.82]
Linko 2011	1.1939	0.9628	72	60	4.6%	3.30 [0.50, 21.78]
Xi 2010	1.3002	0.6685	52	103	6.6%	3.67 [0.99, 13.60]
Subtotal (95% CI)			**540**	**666**	**37.1%**	**2.23 [1.54, 3.24]**
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 4.22 (P < 0.0001)						
Total (95% CI)			**905**	**1307**	**100.0%**	**3.90 [2.31, 6.60]**
Heterogeneity: Tau² = 0.64; Chi² = 43.96, df = 14 (P < 0.0001); I² = 68%						
Test for overall effect: Z = 5.08 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.46, df = 1 (P = 0.06), I² = 71.1%						



Lansbury et al. (2019). Cochrane Database of Systematic Reviews

ARDS SECONDARY TO NON RESPIRATORY CAUSES

Pancreatitis

Trauma SUBPOPULATION TRIALS NOT AVAILABLE

Inhalation injury

CURRENT GUIDELINE RECOMMENDATION

AMERICAN THORACIC SOCIETY DOCUMENTS

An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome

An Official American Thoracic Society Clinical Practice Guideline

Nida Qadir*, Sarina Sahetya*, Laveena Munshi*, Charlotte Summers*, Darryl Abrams, Jeremy Beitler, Giacomo Bellani, Roy G. Brower, Lisa Burry, Jen-Ting Chen, Carol Hodgson, Catherine L. Hough, Francois Lamontagne, Anica Law, Laurent Papazian, Tai Pham, Eileen Rubin, Matthew Siuba, Irene Telias, Setu Patolia, Dipayan Chaudhuri, Allan Walkey‡, Bram Rochwerg‡, and Eddy Fan‡; on behalf of the American Thoracic Society Assembly on Critical Care

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED SEPTEMBER 2023

Question 1: Should Patients with ARDS Receive Systemic Corticosteroids?

Recommendation. We suggest using corticosteroids for patients with ARDS (conditional recommendation, moderate certainty of evidence).

Qadir et al. (2023). American Journal of Respiratory and Critical Care Medicine

2024 FOCUSED UPDATE

Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community Acquired Pneumonia

Society of Critical Care Medicine
The Intensive Care Professionals

POPULATION: Acutely Ill Adult Patients Requiring Hospitalization
(Specific recommendations for pediatric patients are not made.)

Septic Shock	Conditional Recommendation For ↑? Low Certainty of Evidence ⊕⊕◯◯	**1A. We suggest** administering corticosteroids to adult patients with septic shock.
	Strong Recommendation Against ↓↓ Moderate Certainty of Evidence ⊕⊕⊕◯	**1B. We recommend against** administration of high dose/short duration corticosteroids (>400 mg/day hydrocortisone equivalent for less than 3 days) for adult patients with septic shock.
Acute Respiratory Distress Syndrome (ARDS)	Conditional Recommendation For ↑? Moderate Certainty of Evidence ⊕⊕⊕◯	**2A. We suggest** administering corticosteroids to adult hospitalized patients with ARDS.
Community Acquired Pneumonia (CAP)	Strong Recommendation For ↑↑ Moderate Certainty of Evidence ⊕⊕⊕◯	**3A. We recommend** administering corticosteroids to adult patients hospitalized with severe bacterial CAP.*
	No Recommendation Made For explanation, see Full 2024 Focused Update Guidelines linked below.	**3B. We make no recommendation** for administering corticosteroids for adult patients hospitalized with less severe bacterial CAP.*

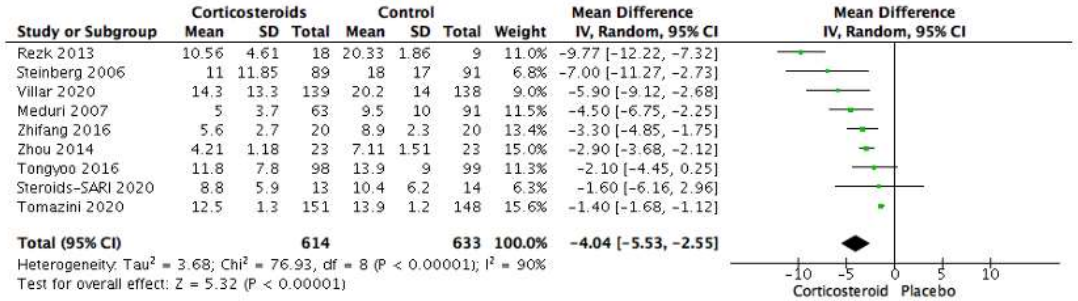
Strength of Recommendation
Strong Recommendation For: ↑↑
Conditional Recommendation For: ↑?
Conditional Recommendation Against: ↓?
Strong Recommendation Against: ↓↓

Certainty of Evidence
Very Low: ⊕◯◯◯
Low: ⊕⊕◯◯
Moderate: ⊕⊕⊕◯
High: ⊕⊕⊕⊕

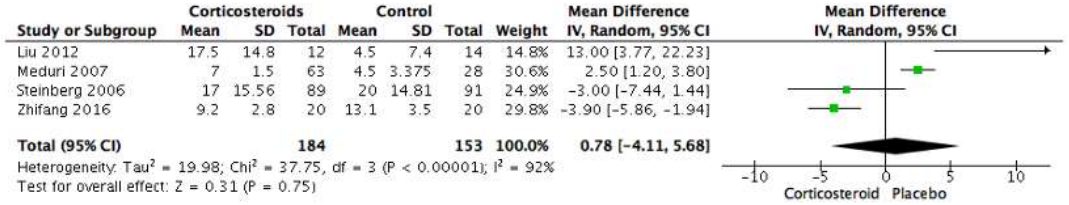
Chaudhuri D, et al. Critical Care Medicine. Online special article. January 19, 2024

SCCM/ESCIM Meta- analysis of ARDS studies

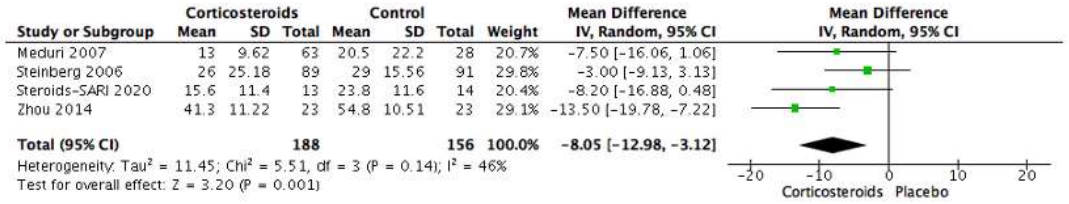
Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Duration of mechanical ventilation. Df = degrees of freedom



Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). ICU length of stay. Df = degrees of freedom



Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Hospital length of stay. Df = degrees of freedom



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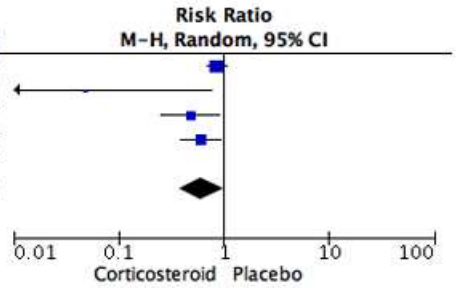
SCCM/ESCIM Meta- analysis of ARDS studies

Forest Plot: ICU mortality. Df = degrees of freedom

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2006	53	85	67	92	40.5%	0.86 [0.70, 1.05]
Meduri 1998	0	16	5	8	2.8%	0.05 [0.00, 0.78]
Meduri 2007	13	63	12	28	24.3%	0.48 [0.25, 0.92]
Villar 2020	26	139	43	138	32.5%	0.60 [0.39, 0.92]
Total (95% CI)		**303**		**266**	**100.0%**	**0.61 [0.38, 0.99]**
Total events	92		127			

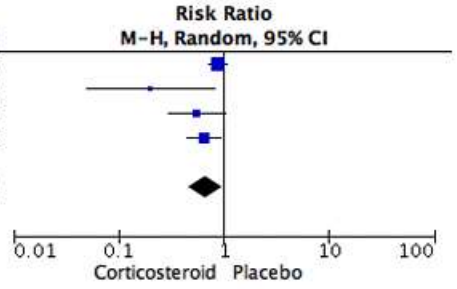
Heterogeneity: Tau² = 0.13; Chi² = 9.65, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 2.01 (P = 0.04)



Forest Plot: Hospital mortality. Df = degrees of freedom

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2006	54	85	67	92	41.6%	0.87 [0.71, 1.07]
Meduri 1998	2	16	5	8	6.0%	0.20 [0.05, 0.81]
Meduri 2007	15	63	12	28	20.4%	0.56 [0.30, 1.03]
Villar 2020	33	139	50	138	32.1%	0.66 [0.45, 0.95]
Total (95% CI)		**303**		**266**	**100.0%**	**0.67 [0.46, 0.96]**
Total events	104		134			

Heterogeneity: Tau² = 0.07; Chi² = 7.47, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 2.18 (P = 0.03)



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2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

Corticosteroid Dosing Regimens

Disease State	Common Corticosteroid Regimens
Septic shock	Hydrocortisone 200 mg IV per day (continuous infusion or divided every 6 hr) with or without fludrocortisone 50 µg enteral daily for 7 d or until ICU discharge[a]
ARDS	Early ARDS (within 24 hr) Dexamethasone 20 mg IV daily for 5 d, then 10 mg IV daily for 5 d until extubation (64) Early ARDS (within 72 hr) (65) Methylprednisolone 1 mg/kg IV bolus, then • Days 1–14: 1 mg/kg/d continuous infusion • Days 15–21: 0.5 mg/kg/d • Days 22–25: 0.25 mg/kg/d • Days 26–28: 0.125 mg/kg/d • If extubated between days 1 and 15 then advance to day 15 of regimen Unresolving ARDS (7–21 d) (26) Methylprednisolone 2 mg/kg IV bolus, then • Days 1–14: 2 mg/kg/d divided every 6 hr • Days 15–21: 1 mg/kg/d • Days 22–28: 0.5 mg/kg/d • Days 29–30: 0.25 mg/kg/d • Days 31–32: 0.125 mg/kg/d • If extubated before day 14, then advance to day 15 of regimen drug therapy

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Controversies and uncertainties

- No prospective RCTs after 2020 on non-covid ARDS (DEXA ARDS study)
- Last methylprednisolone study in 2016, suggesting a gap in newer data on this corticosteroid for ARDS treatment.
- **Guidelines based on older studies**: ARDS SCCM guidelines 2024, are still primarily based on older studies (including some from 1998) and ,metanalysis with smaller sample sizes. These studies may not reflect the most current evidence or methodologies.

ONGOING TRIALS

Glucocorticoids in adults with Acute Respiratory Distress Syndrome (GuARDS Trial)

GUARDS
GlUcocorticoids for ARDS

Start Date:
June 2023

End Date:
May 2028

Contracting Organisation:
The University of Edinburgh

The Corticosteroid Early and Extended (CORT-E^2) Randomized Controlled Trial

Protocol Version #:	3.0
Protocol Date:	27-Jun-2024

Can steroids be given for ARDS?

- **Yes,** corticosteroids could be considered for ARDS, particularly when given within 14 days of symptom onset, based on available meta-analyses.
- **But** there is a clear need for larger trials with head-to-head comparisons between methylprednisolone, dexamethasone, and hydrocortisone to confirm their efficacy in ARDS treatment.
- **Future Trials:** More well-powered studies with subgrouping of Pulmonary / extrapulmonary cases and comparison of steroids are needed to refine treatment protocol.

How we could apply?

- ARDS patient with PaO2/Fio2< 200 mmhg
- Pneumonia with ARDS and Sepsis with ARDS
- Choice of steroids : Dexamethasone /Methylprednisolone
- To be avoided in late ARDS and in patients with Influenza
- Role of CRP as signal for steroid responsive patient in ARDS were not studied
- Evidence are limited to show increase in side effects except hyperglycaemia
- Bit dubious whether steroid would be beneficial, in the context of trauma
- Blanket statement " STEROID IS BENEFICIAL IN ARDS " – LACKS VALIDITY

THANK YOU