STEROIDS IN CAP

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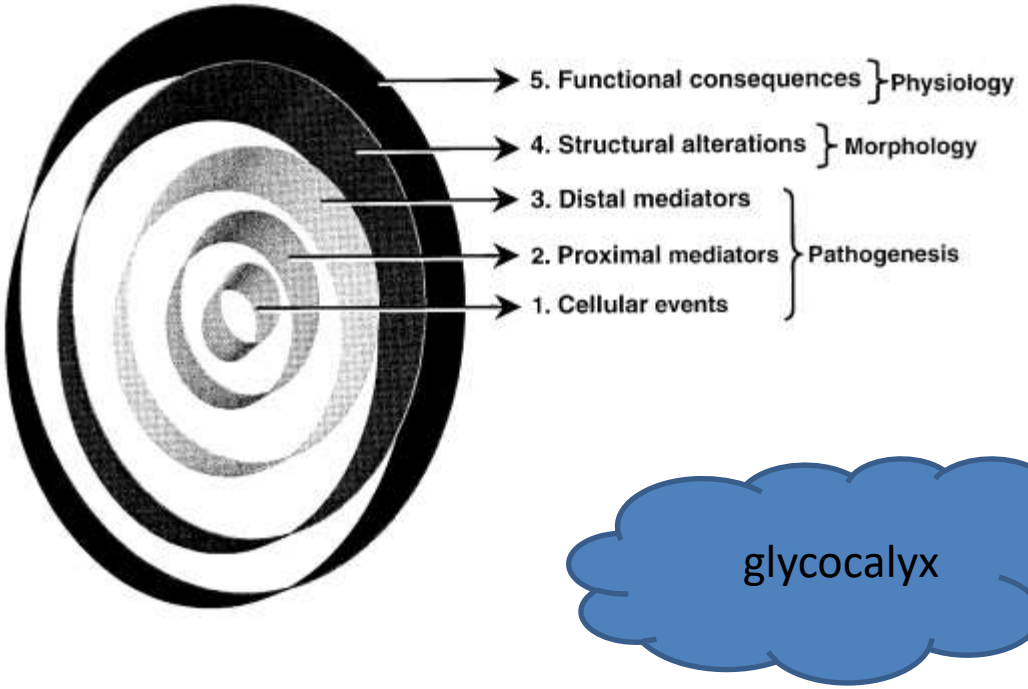


I. Factors associated with the investigated treatment
- A. Disease pathophysiological model dictating treatment design
- B. Treatment directed at a central vs peripheral pathogenetic process
- C. Treatment positively modifies disease pathogenesis
- D. Treatment-associated complications*
- E. Treatment effect is sustained until disease resolution.

II. Factors associated with the precipitating insult
- A. Rapid and correct diagnosis
- B. Appropriate specific treatment

III. Factors associated with the patient
- A. Severity of chronic underlying illness
- B. Age
- C. Sex
- D. Others

IV. Factors other than treatment
- A. Disease severity and duration
- B. Development of complications not related to treatment
- C. Adequacy of support for vital organs
- D. Appropriate recognition and treatment of nosocomial infections

- Over activity of transcription factors NF-kB vs Glucocorticoid alpha receptor (G-GRα) complex
- Cytokines TNF-a, IL-1b, and other mediators directly transcribed by the activated transcription factors NF-kB – pro inflammatory markers
- The host defense response peripheral pathways—inflammation, coagulation, and tissue repair—that affect tissue level changes

https://doi.org/10.1023/A:1009870524359 https://doi.org/10.1186%2F2110-5820-1-7

- Pro-inflammatory mediators recruit the HPA axis to counter-regulate inflammation through the synthesis of the stress hormone cortisol
- There is increase in cortisol after administration of exogenous corticosteroid
- Increased cortisol promotes hemodynamic stability by increasing MAP & SVR and modifies CVS response to inflammation
- Suppressed IL-6 , IL-8 and other pro-inflammatory mediators
- Decreases overwhelming increase in anti inflammatory mediators
- The effect on T cells, monocytes, Th1 – Th2 interaction/switching - *complex*

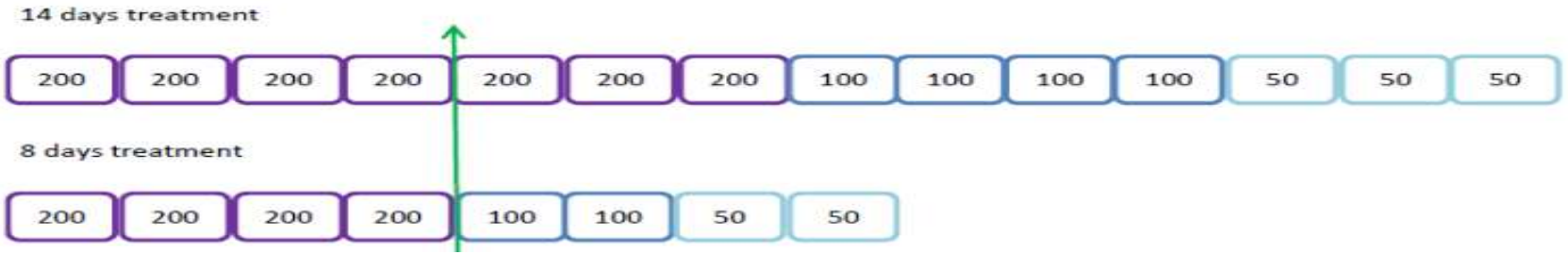
Protection from overshooting inflammatory response vs possible aggravated immune – suppression

https://doi.org/10.1164/rccm.200205-446OC AJRCCM 2002

Hydrocortisone in Severe Community-Acquired Pneumonia

P.-F. Dequin, F. Meziani, J.-P. Quenot, T. Kamel, J.-D. Ricard, J. Badie, J. Reignier, N. Heming, G. Plantefève,

- Multicenter, double-blind, RCT, severe CAP (not influenza),ICU,
- Hcort within 24hrs (200mg for 4/7 days taper to 8-14days) vs placebo (1:1)
- To taper⬇ SOFA, p/f>200, spontaneous breathing, discharge from ICU- D14
- N=795 , stopped after 2nd interim analysis (stopped during COVID)
- Pneumonia : **MV**/ **NRBM** or **HFNC** (p/f<300+fio2 50%)/ **PSI – 5**
- **Exclusion : shock at time of inclusion, fungal/TB/cystic fibrosis/ steroids at baseline / influenza / immune- suppressed**



Dequin PF et.al.,Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023 May 25;388(21

Characteristic	Hydrocortisone (N=400)	Placebo (N=395)
Median age (IQR) — yr	67 (58–77)	67 (58–78)
Sex — no. (%)		
Male	281 (70.2)	271 (68.6)
Female	119 (29.8)	124 (31.4)
Coexisting condition — no. (%)		
COPD	86 (21.5)	105 (26.6)
Asthma	22 (5.5)	17 (4.3)
Diabetes	95 (23.8)	86 (21.8)
Immunosuppression	24 (6.0)	27 (6.8)
Type of respiratory support — no. (%)		
Mechanical ventilation	178 (44.5)	175 (44.3)
Invasive	92 (23.0)	85 (21.5)
Noninvasive	86 (21.5)	90 (22.8)
High-flow nasal cannula	169 (42.2)	162 (41.0)
Nonrebreathing mask	53 (13.2)	58 (14.7)
Median Pulmonary Severity Index (IQR)†	127 (102–153)	130 (103–150)
Distribution — no./total no. (%)		
Class I	5/396 (1.3)	4/392 (1.0)
Class II	15/396 (3.8)	15/392 (3.8)
Class III	45/396 (11.4)	47/392 (12.0)
Class IV	150/396 (37.9)	133/392 (33.9)
Class V	181/396 (45.7)	193/392 (49.2)
Median SAPS II score (IQR)‡	37 (30–45)	38 (31–47)
Median SOFA score (IQR)§	4 (3–6)	4 (3–6)
Treatment with vasopressors — no. (%)	41 (10.2)	51 (12.9)
Laboratory data		
C-reactive protein		
Median (IQR) — mg/dl	26.3 (11.7–35.6)	23.8 (11.7–35.0)
Value of >15 mg/dl — no./total no. (%)	208/298 (69.8)	215/312 (68.9)
Median procalcitonin (IQR) — ng/ml	3.2 (0.5–16.4)	4.1 (0.6–16.0)
Median cortisol (IQR) — nmol/liter	302 (24–785)	307 (25–697)
Timing of treatment		
Median interval from hospital admission to ICU admission (IQR) — hr	5.5 (2.8–10.9)	5.2 (2.4–10.9)
Median interval from ICU admission to initiation of trial agent (IQR) — hr	15.3 (7.0–20.5)	14.6 (5.9–20.5)

	Hydrocortisone (n_1=400)	Placebo (n_2=395)
No pathogen identified, No. (%)	189 (47.2)	168 (42.5)
At least one pathogen identified, No. (%)	211 (52.7)	227 (57.5)
Streptococcus pneumoniae, No. (%)	83 (23.8)	82 (20.8)
Legionella sp., No. (%)	22 (5.5)	29 (7.3)
Staphylococcus aureus, No. (%)	16 (4.0)	24 (6.1)
Haemophilus influenzae, No. (%)	15 (3.8)	20 (5.1)
Non-pneumoniae Streptococci	13 (3.3)	12 (3.0)
Escherichia coli, No. (%)	13 (3.3)	11 (2.8)
Klebsiella pneumoniae, No. (%)	11 (2.8)	6 (1.5)
Coagulase-negative Staphylococci	11 (2.8)	4 (1.0)
Chlamydia sp., No. (%)	4 (1.0)	6 (1.5)
Pseudomonas aeruginosa	4 (1.0)	5 (1.3)
Mycoplasma pneumoniae, No. (%)	3 (0.8)	7 (1.8)
Other bacteria, No. (%)	28 (7.1)	32 (8.1)
Myxovirus influenzae, No. (%)	12 (3.0)	12 (3.0)
Rhinovirus	9 (2.3)	6 (1.5)
Respiratory syncyticial virus	5 (1.3)	6 (1.5)
Other respiratory viruses, No. (%)	13 (3.0)	4 (1.0)
Fungi and yeasts	2 (0.5)	6 (1.5)
Antibiotics administered since admission		
Third-generation cephalosporins, No. (%)	310 (77.5)	317 (80.3)
Macrolides, No. (%)	289 (72.3)	298 (75.4)
Amoxicillin, No. (%)	90 (22.5)	72 (18.2)
Amoxicillin – Clavulanic acid, No. (%)	79 (19.8)	69 (17.5)
Fluoroquinolones, No. (%)	64 (16.0)	68 (17.2)
Other antibiotics, No. (%)	120 (30.0)	135 (34.2)

- 1st analysis : On day 28, death occurred in 11 out of 196 patients (5.6%; 95% CI, 2.4 to 8.8) in the hydrocortisone group and in 27 out of 202 patients (13.4%; 95% CI, 8.7 to 18.1) in the placebo group (crude difference -7.8%; 95% CI -13.4 to -2.1; p=0.0085)
- In the second interim analysis, the DSMB recommended to definitively stop the inclusions, considering

  1st that the inclusion of the last 400 planned patients would most likely not change the results,

  2nd that it became ethically unacceptable to continue to include in the placebo group,

  3rd that the prolonged suspension of the inclusions due to the COVID-19 pandemic would probably complicate the resumption of inclusions

Outcome	Hydrocortisone	Placebo	Treatment Effect (95% CI)	P Value
Primary outcome				
Death by day 28 — no./total no. (%)	25/400 (6.2)	47/395 (11.9)	Difference, −5.6	0.006
95% CI — percentage points	3.9 to 8.6	8.7 to 15.1	−9.6 to −1.7	
Secondary outcomes†				
Death by day 90 — no./total no.	36/388 (9.3)	57/389 (14.7)	Difference, −5.4	
95% CI — percentage points	6.4 to 12.2	11.1 to 18.2	−9.9 to −0.8	
Patients not receiving any mechanical ventilation at baseline — no./total no. (%)				
Cumulative incidence of endotracheal intubation by day 28	40/222 (18.0)	65/220 (29.5)	HR, 0.59 (0.40 to 0.86)	
Cumulative incidence of noninvasive ventilation by day 28	15/222 (6.8)	24/220 (10.9)	HR, 0.60 (0.32 to 1.15)	
Cumulative incidence of endotracheal intubation by day 28 in patients not receiving endotracheal intubation at baseline — no./total no. (%)	60/308 (19.5)	86/310 (27.7)	HR, 0.69 (0.50 to 0.94)	
Cumulative incidence of initiation of vasopressors by day 28 in patients not receiving vasopressor at baseline — no./total no. (%)	55/359 (15.3)	86/344 (25.0)	HR, 0.59 (0.43 to 0.82)	
Safety outcomes‡				
Cumulative incidence of hospital-acquired infection by day 28 — no./total no. (%)§	39/400 (9.8)	44/395 (11.1)	HR, 0.87 (0.57 to 1.34)	0.54
Ventilator-associated pneumonia	32/152 (21.0)	38/171 (22.2)		
Bloodstream infection	5/400 (1.2)	9/395 (2.3)		
Cumulative incidence of gastrointestinal bleeding by day 28	9/400 (2.2)	13/395 (3.3)	HR, 0.68 (0.29 to 1.59)	0.38
Median daily dose of insulin by day 7 in patients receiving insulin therapy (IQR) — IU/day¶	35.5 (15.0 to 57.5)	20.5 (9.4 to 48.5)	Median difference, 8.7 (4.0 to 13.8)	<0.001

	Hydrocortisone (n_1=400)	Placebo (n_2 =395)
Actual duration of experimental treatment, median [IQR], days	5 [3; 8]	6 [3; 8]
Premature stopping, No. (%)	318 (79,5)	298 (75,4)
Reasons for premature stopping		
Influenza diagnosed after randomization, No. (%)	12 (3.8)	12 (4.0)
Indication for open-label corticosteroid therapy, No. (%)	17 (5.3)	23 (7.7)
Withdrawal from the trial at the patient's request, No. (%)	4 (1.3)	1 (0.3)
Discharge alive from the intensive care unit, No. (%)	261 (82.1)	220 (73.8)
Death before the planned end of the experimental treatment, No. (%)	24 (7.5)	42 (14.1)

- Did not achieve the target sample as terminated early
- Screened 6000 patients , maintained robust inclusion criteria
- Benefit in mortality, intubation, vasopressor requirement with no increase in severe side effects / HAP / VAP / BSI
- Expected mortality of 27% in placebo but actual of 11%
- Early hydrocortisone beneficial in severe CAP
- Structural lung disease patients ??
- Etiological organisms in 47%
- CRP levels stratification & survival sub group analysis has not been provided
- Severity wise mortality sub group analysis ?

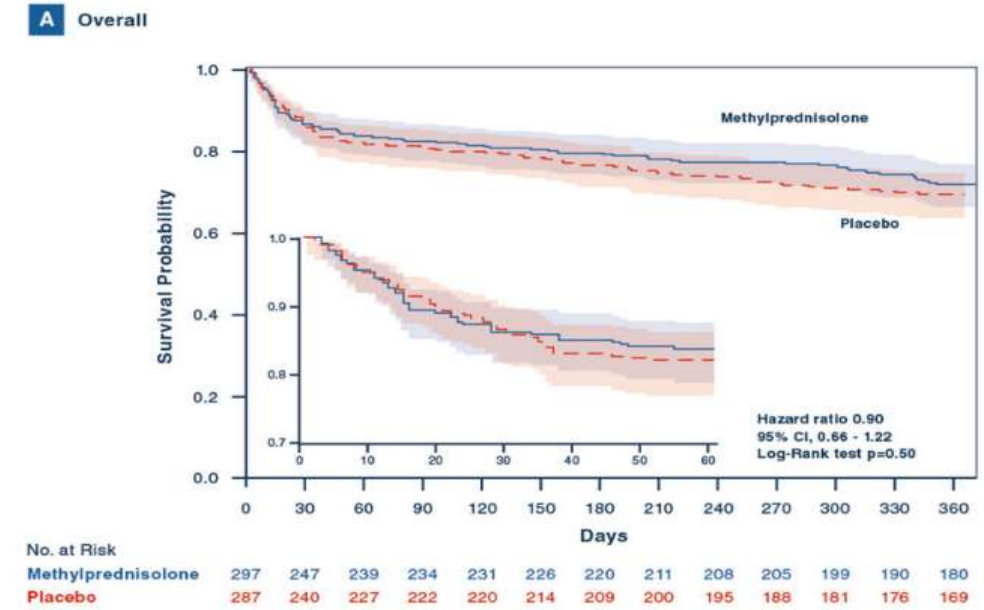
Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia

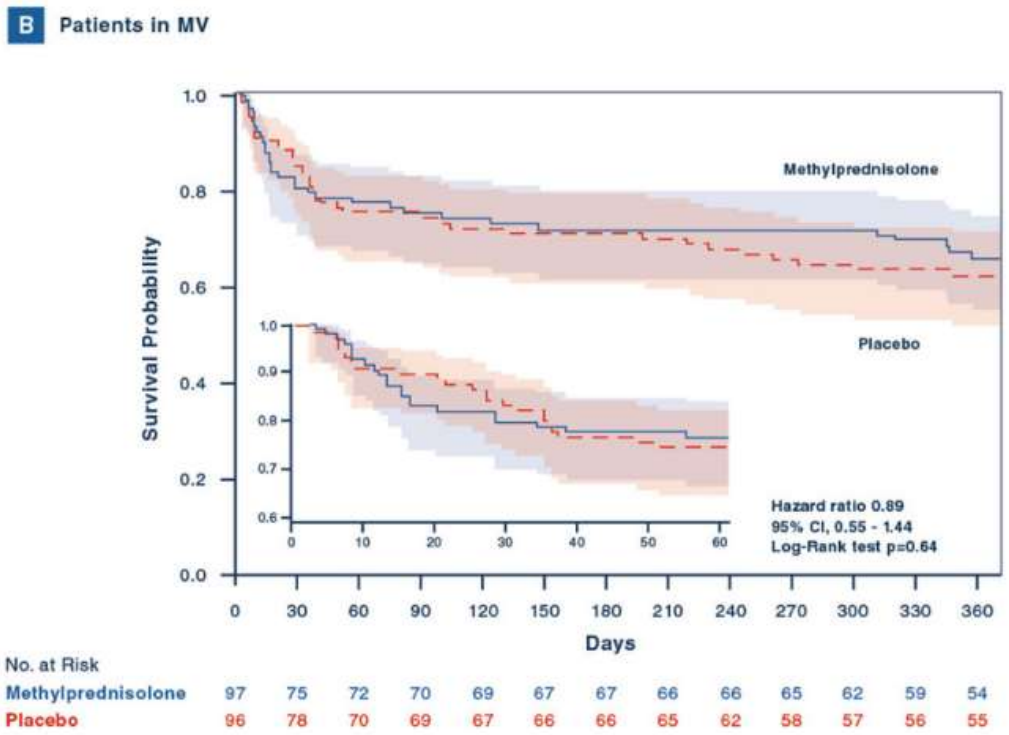
G. Umberto Meduri[1,2*], Mei-Chiung Shih[3,4], Lisa Bridges[1,2], Thomas J. Martin[5,6,7], Ali El-Solh[8,9], Nitin Seam[10],

- Multicenter, double-blind, RCT, 2012-16, veterans only, admitted to ICU
- CAP / HCAP – 4-5days after admission to ICU/intermediate care
- ATS – IDSA – one major or 3 minor criteria
- MPS infusion : 40mg D1-7, 20 mg D8–14, 12 mg D15–17 , 4 mg D18–20
- Study terminated due to low recruitment, target was to show 7% mortality difference (28% placebo vs 21%MPS) (n-584, target 1400, screened 4K)
- Median time to initiate treatment after hospitalization : 40hrs
- No difference in short term / long term mortality or side effect profile

Meduri Guetal.,; ESCAPe Study Group. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med. 2022 Aug;48

Characteristic	Methylprednisolone (*n* = 297)	Placebo (*n* = 287)
HCAP—no./total no. (%)	112/297 (38)	89/287 (31)
Resided in nursing home or long-term care facility immediately prior to hospital admission	40/297 (13)	48/287 (17)
Hospitalized in acute care hospital for 2 or more days within past 90 days	81/297 (27)	58/287 (20)
Received intravenous therapy (antibiotic or chemotherapy) within past 30 days	42/297 (14)	31/287 (11)
Received home wound care within past 30 days	18/297 (6)	13/287 (5)
Received hemodialysis within past 30 days	10/297 (3)	8/287 (3)
Admission from the ward—no. (%)	66/297 (22)	57/287 (20)
PSI class—no. (%)		
I	3/297 (1)	4/285 (1)
II	13/297 (4)	13/285 (5)
III	41/297 (14)	29/285 (10)
IV	121/297 (41)	126/285 (44)
V	119/297 (40)	113/285 (40)
PIRO	2.14 ± 1.12	2.15 ± 1.1
CURB-65	2.69 ± 1.03	2.59 ± 1.03
Chest Radiograph Score	2.09 ± 1.02	1.94 ± 1.08
Bilateral—no./total no. (%)	189/288(66)	163/276 (59)
Multilobar—no./total no. (%)	216/297 (73)	188/285 (66)
PaO_2/FiO_2 (if PaO_2 is available)[a]	181 ± 85	188 ± 90
SpO_2/FiO_2 (if PaO_2 is not available)[b]	283 ± 101	286 ± 98
APACHE III Score	54.3 ± 29.4	53.4 ± 28.7
SAPS III Score	59.4 ± 10.7	58.5 ± 9.9
SOFA Score	6.68 ± 3	6.29 ± 2.85
Lactate level (mmol/L)[c]	1.84 ± 1.25	1.82 ± 1.81
MV at study entry—no./total no. (%)	97/297 (33)	96/287 (33)
Vasopressor dependent Shock at or prior to study entry—no./total no. (%)	44/296 (15)	32/285 (11)





no significant difference in 60-day mortality (16%(MPS) vs. 18%; p=0.61)

similar 180-day mortality (21% vs. 24%; OR 0.86; 95% CI 0.58–1.29; p=1.00)

no significant differences between the treatment groups in development of vasopressor-dependent shock, development of ARDS, MV-free days up to days 8 or 28, duration of ICU/hospital stay

participants who required MV at randomization, there was a 3-day reduction in median duration of MV (median 4 vs. 7 days; hazard ratio (HR) 1.44; 95% CI 1.04–1.99; p=0.21)

- Did not achieve the target sample (target 1400)
- HCAP (34%) patients included, 10% patients had influenza
- No increase in side effect profile & no mortality difference
- Delayed initiation of steroids – 40 hrs
- Sub set of patients in shock at the time of inclusion – 15%
- Structural lung disease patients ??
- Severity wise mortality sub group analysis is not yet provided
- CRP stratification and mortality analysis is yet to come

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response
A Randomized Clinical Trial

- Severe CAP by modified ATS/ PSI -5 and CRP > 150mg/L, no influenza
- **IV MPS 0.5mg/kg BD** vs **placebo** x 5days, started within 36 hours
- 35% treatment failure in placebo group and 20% decrease by steroids
- Early treatment failure was defined as clinical deterioration within 72 hours of treatment (included development of shock, need for invasive mechanical ventilation not present at baseline, or death).
- Late treatment failure was defined as radiographic progression (increase of ≥50% of pulmonary infiltrates), persistence of severe respiratory failure (ratio of PaO2/FiO2<200 mm Hg, with respiratory rate ≥30 breaths/min in patients not intubated), / shock / MV / death

Torres A etal., Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015 Feb 17;

Baseline Characteristics of the Intention-to-Treat Population

	Methylprednisolone (n = 61)	Placebo (n = 59)
Pneumonia Severity Index score, mean (SD)[17]	107 (38)	110 (35)
Risk class, No. (%)[c]		
I-III	18 (30)	14 (24)
IV	21 (34)	26 (44)
V	22 (36)	19 (32)
Major severity criteria,[16] No. (%)[d]		
Mechanical ventilation	5 (8)	10 (17)
Noninvasive alone	3 (5)	5 (8)
Noninvasive followed by invasive	1 (2)	3 (5)
Invasive alone	1 (2)	2 (3)
Septic shock	10 (17)	18 (31)
Minor severity criteria, No. (%)[16]		
Systolic blood pressure <90 mm Hg	11 (18)	17 (29)
Multilobar involvement	37 (61)	34 (58)
Ratio of $Pa0_2$ to fraction of inspired oxygen <250 mm Hg, No. (%)	42 (70)	40 (68)
ICU admission, No. (%)	43 (70)	47 (80)
C-reactive protein, mg/L[b]	273 (202-292)	244 (172-289)
Procalcitonin, ng/dL[b]	1.3 (0.4-4.4)	3.1 (0.8-9.5)
IL-6, pg/dL[b]	256 (133-674)	316 (182-834)
IL-8, pg/dL[b]	74 (34-107)	88 (55-182)
IL-10, pg/dL[b]	4.7 (2.8-9.2)	8.1 (4.0-13.5)

	Intention-to-Treat Population				Per-Protocol Population			
	Methylprednisolone Group (n = 61)	Placebo Group, (n = 59)	*P* Value	Difference Between Groups, % (95% CI)	Methylprednisolone Group (n = 55)	Placebo Group (n = 57)	*P* Value	Difference Between Groups, % (95% CI)
Primary Clinical Outcome								
Treatment failure, No. (%)[a]	8 (13)	18 (31)	.02	18 (3 to 32)	5 (9)	16 (28)	.01	19 (5 to 33)
Early treatment failure (0-72 h), No. (%)[b]	6 (10)	6 (10)	.95	0 (−10 to 11)	3 (5)	4 (7)	>.99	2 (−7 to 11)
Early mechanical ventilation	4 (7)	5 (8)	.74	2 (−8 to 11)	2 (4)	3 (5)	>.99	2 (−6 to 9)
Early septic shock	2 (3)	3 (5)	.68	2 (−5 to 9)	1 (2)	2 (4)	>.99	2 (−4 to 8)
Death	2 (3)	2 (3)	>.99	0 (−6 to 7)	0	0		
Late treatment failure (72-120 h), No. (%)[b]	2 (3)	15 (25)	.001	22 (10 to 34)	2 (4)	14 (25)	.002	21 (9 to 33)
Radiographic progression	1 (2)	9 (15)	.007	14 (4 to 23)	1 (2)	8 (14)	.03	12 (3 to 22)
Respiratory failure	1 (2)	5 (8)	.11	7 (−1 to 15)	1 (2)	5 (9)	.21	7 (−1 to 15)
Late mechanical ventilation	1 (2)	4 (7)	.20	5 (−2 to 12)	1 (2)	4 (7)	.36	5 (−2 to 13)
Late septic shock	0	4 (7)	.06	7 (0 to 13)	0	4 (7)	.12	7 (0 to 14)
Death	0	0			0	0		
Secondary Clinical Outcomes								
Time to clinical stability, median (IQR), d[c]	4 (3 to 6)	5 (3 to 7)	.28	1 (−0.4 to 2.4)	4 (3 to 6)	5 (3 to 7)	.13	1 (0 to 2)
Length of stay, median (IQR), d								
Hospital	11 (7.5 to 14)	10.5 (8 to 15)	.83	−0.5 (−4.6 to 3.6)	11 (8 to 14)	11.5 (8 to 15)	.70	0.5 (−3.3 to 4.3)
ICU[d]	5 (3 to 8)	6 (4 to 8)	.63	1 (−0.4 to 2.4)	5 (3 to 8)	6 (4 to 8)	.38	1 (0 to 2)
In-hospital mortality, No. (%)	6 (10)	9 (15)	.37	5 (−6 to 17)	3 (5)	7 (12)	.21	7 (−4 to 17)

- Completed their target size, Steroid use within 36 hrs
- They assumed that reduced treatment failure should reduce mortality as in their previous studies they saw 25% mortality in treatment failure cases
- 1st hr Abx in 20-30% patients , within 4 hrs in 75- 80% patients
- Late treatment failure decreased with steroids , radiographic progression
- Although 18% reduction in treatment failure but no mortality benefit
- Included patients with CRP levels > 150mg/L

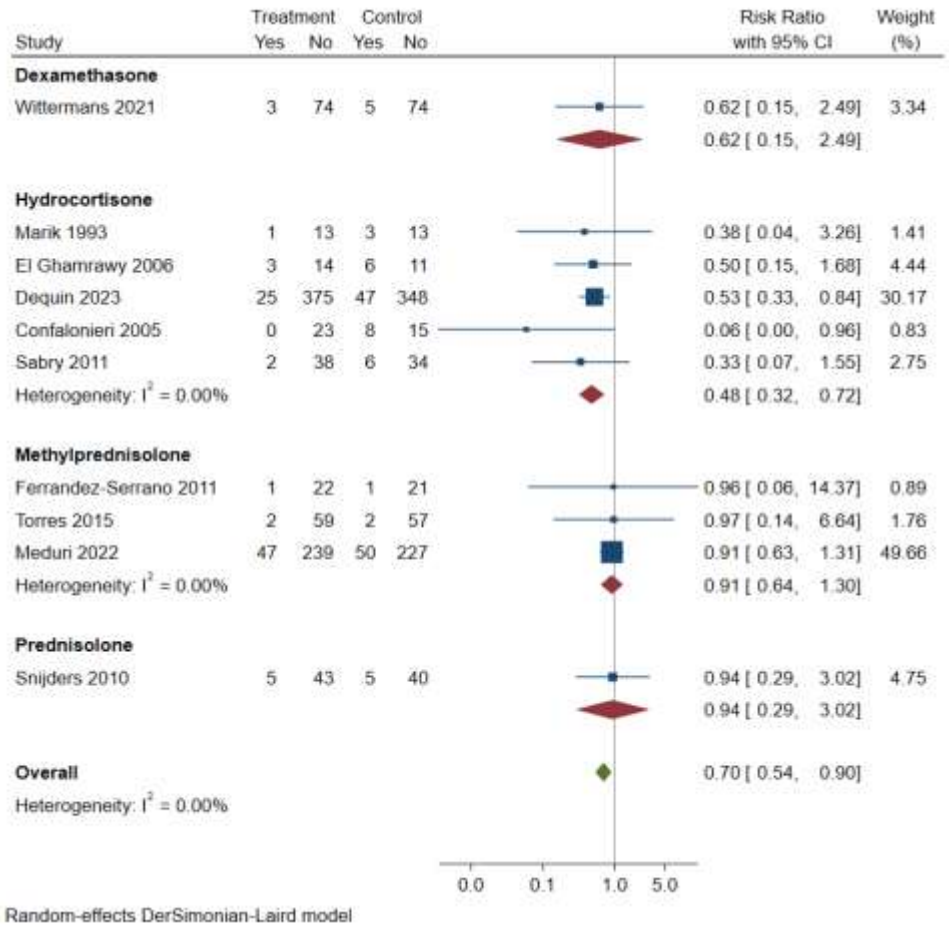
Dequin 2023	**795 patients Severe CAP**	**Hydrocortisone 200mg/day for D8/D14**	**Mortality D28, 6.2% vs 11.9% (absolute difference -5.6 % points, 95% CI , -9.6 to -1.7) P=0.006**	**NNT = 18 to prevent 1 death at D28**
Meduri 2022	584 severe CAP veterans	MPS 40mg/day for 7 days → taper till D20	Mortality at D60 no difference , but no increase in side effect profile	NNT = 50 to prevent 1 death at D60
Torres 2015	120 severe CAP + CRP > 150mg/dl	MPS iv 0.5mg/kg BD for 5 days	Treatment failure 13% vs 31% (P=0.02)	NNT = 6 to prevent 1 treatment failure

BMJ Open Respiratory Research

Impact of different corticosteroids on severe community-acquired pneumonia: a systematic review and meta-analysis

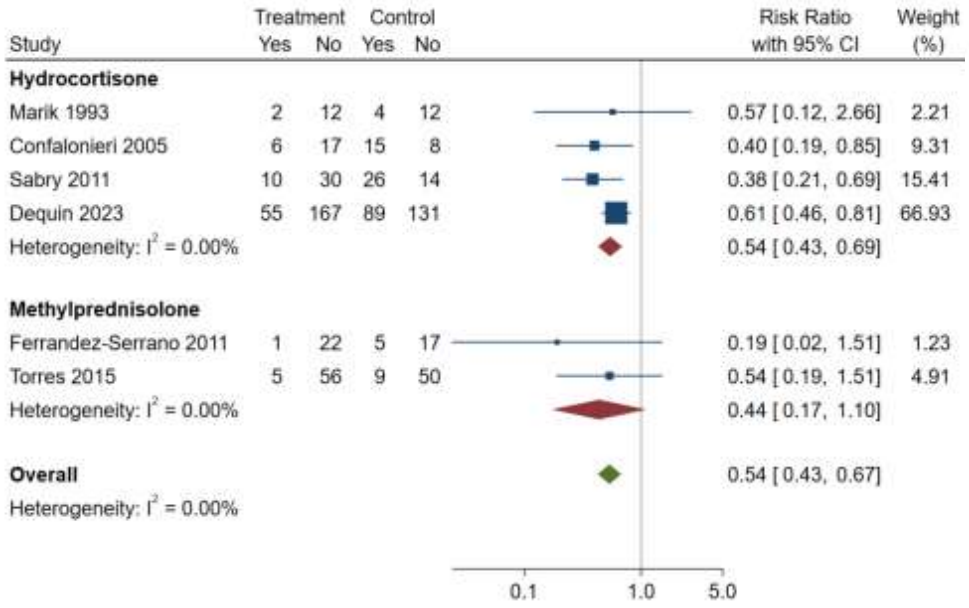
- Included RCTs with severe CAP and oral/iv steroids
- PSI 4/5, ATS IDSA, CURB - 65>2, BTS , development of respiratory failure by P/F < 300 or ICU admission.
- 9 double blind RCT + one open label, 5 HCS, DXM 1, MPS 3 , PS 1 trial
- Total patients – 1962
- Hydrocortisone was found superior to other steroids in terms of mortality benefit , reduction in mechanical ventilation, ARDS, shock and duration of stay in the ICU
- Hydrocortisone beneficial in severe CAP patients
- No statistically significant increase in side effect profile

doi: 10.1136/bmjresp-2023-002141

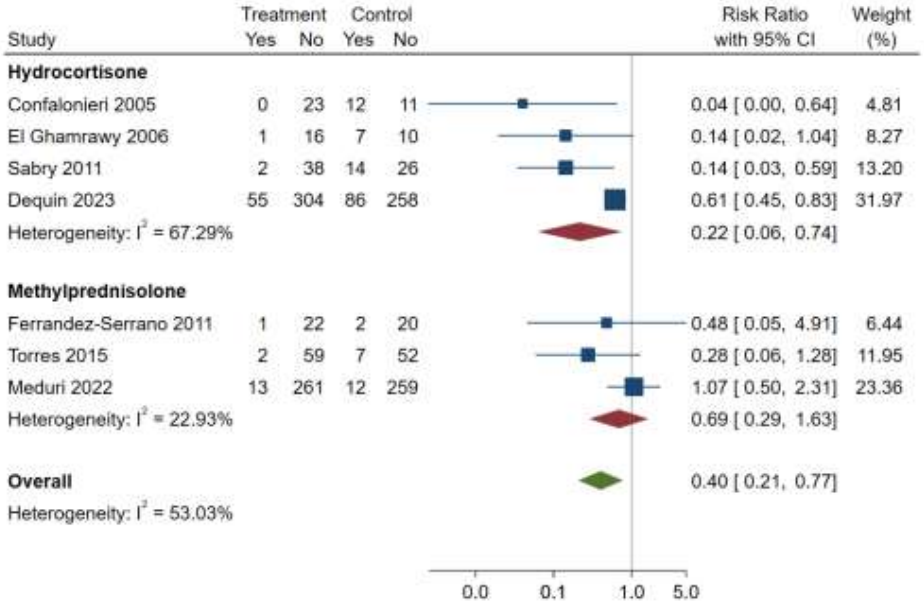


Effect of corticosteroids on all cause mortality

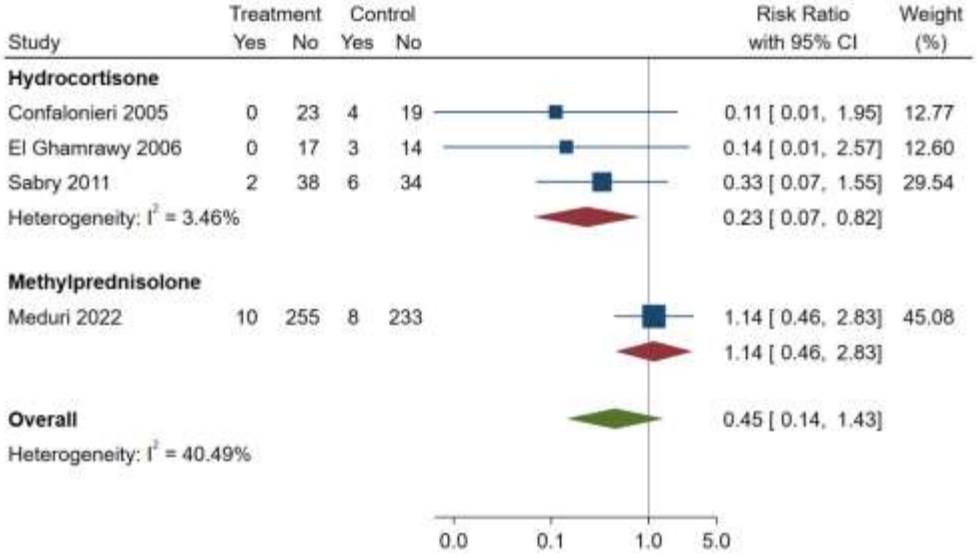
- All steroids : 30% lower rate of all-cause mortality compared with placebo (RR, 0.70 (95% CI 0.54 to 0.90)
- Hydrocortisone : 50% lower mortality risk as compared with placebo (RR, 0.48 (95% CI 0.32 to 0.72)



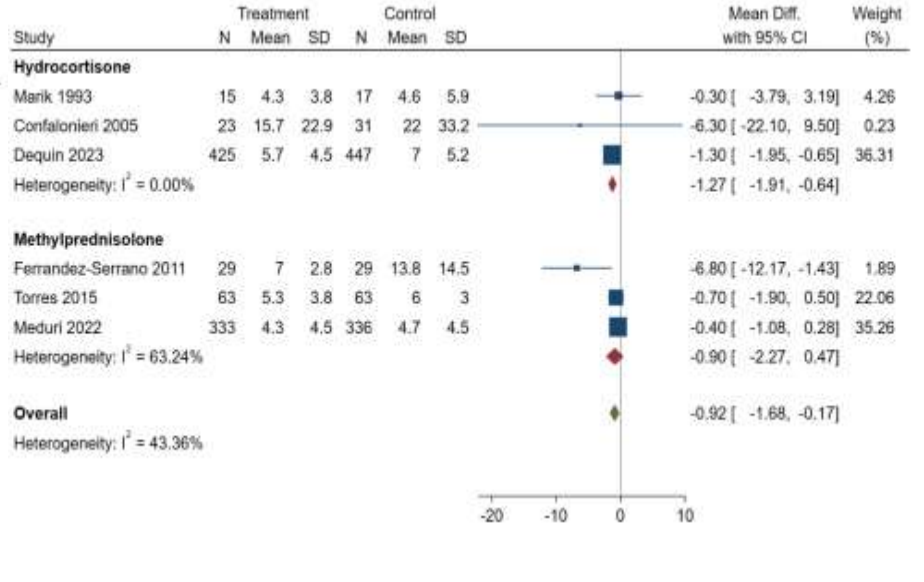
Mechanical ventilation



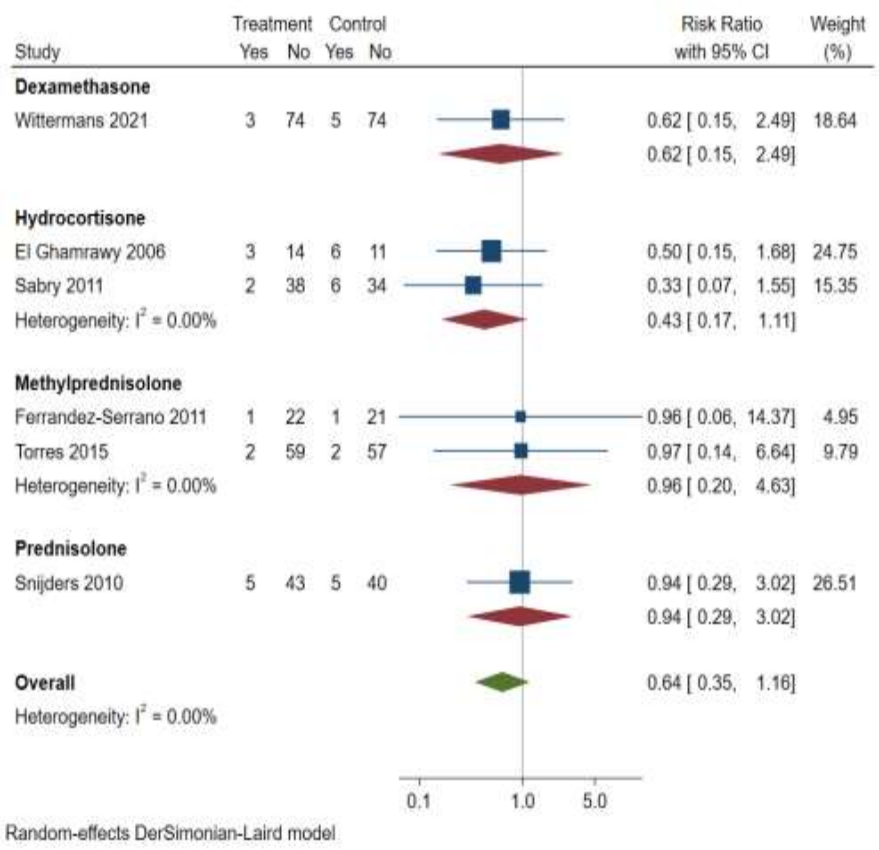
Risk of shock

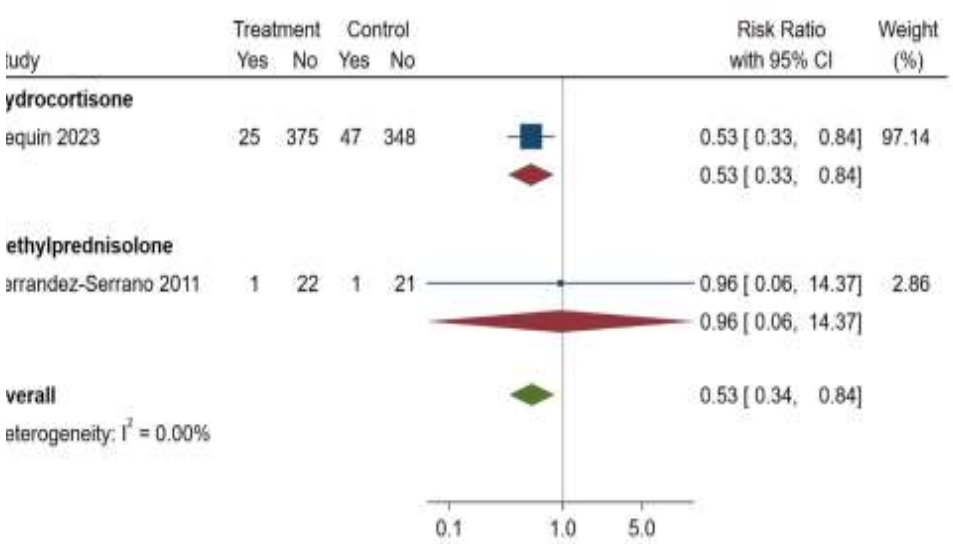


ARDS



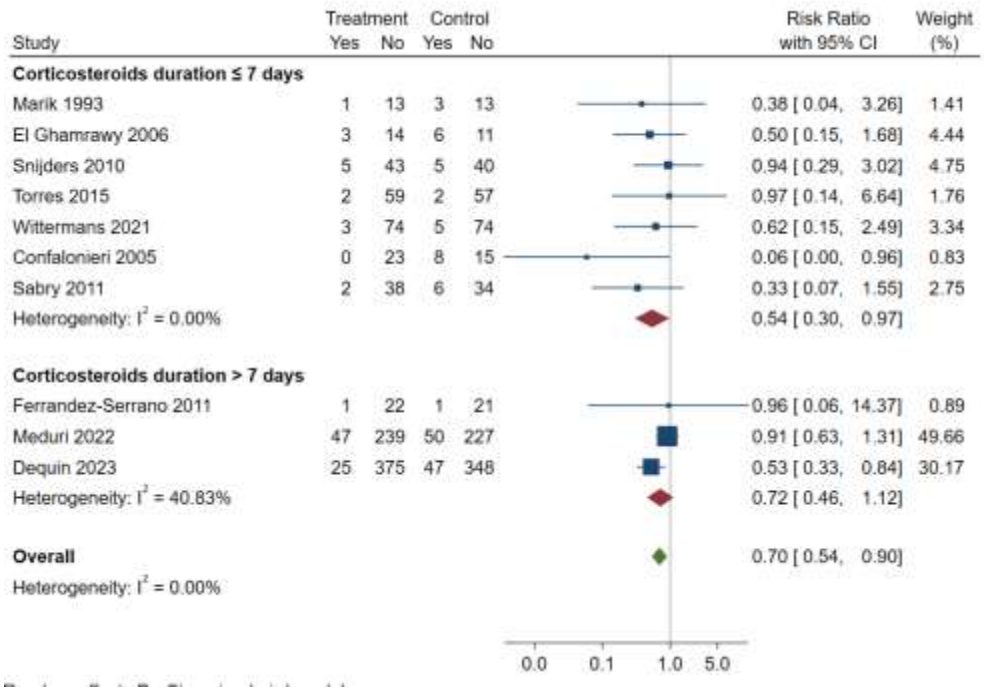
ICU stay





Sensitivity analysis after exclusion of studies that only included patients admitted to the ICU

Sensitivity analysis with studies that excluded patients with sepsis or septic shock.


Study
Treatment Yes No
Control Yes No
Risk Ratio with 95% CI
Weight (%)
Corticosteroids duration ≤ 7 days
Marik 1993 1 13 3 13 0.38 [0.04, 3.26] 1.41
El Ghamrawy 2006 3 14 6 11 0.50 [0.15, 1.68] 4.44
Snijders 2010 5 43 5 40 0.94 [0.29, 3.02] 4.75
Torres 2015 2 59 2 57 0.97 [0.14, 6.64] 1.76
Wittermans 2021 3 74 5 74 0.62 [0.15, 2.49] 3.34
Confalonieri 2005 0 23 8 15 0.06 [0.00, 0.96] 0.83
Sabry 2011 2 38 6 34 0.33 [0.07, 1.55] 2.75
Heterogeneity: I^2 = 0.00% 0.54 [0.30, 0.97]
Corticosteroids duration > 7 days
Ferrandez-Serrano 2011 1 22 1 21 0.96 [0.06, 14.37] 0.89
Meduri 2022 47 239 50 227 0.91 [0.63, 1.31] 49.66
Dequin 2023 25 375 47 348 0.53 [0.33, 0.84] 30.17
Heterogeneity: I^2 = 40.83% 0.72 [0.46, 1.12]
Overall 0.70 [0.54, 0.90]
Heterogeneity: I^2 = 0.00%
0.0
0.1
1.0
5.0

Hydrocortisone Infusion for Severe Community-acquired Pneumonia

A Preliminary Randomized Study

Marco Confalonieri, Rosario Urbino, Alfredo Potena, Marco Piattella, Piercarlo Parigi, Giacomo Puccio, Rossana Della Porta, Carbone Giorgio, Francesco Blasi, Reba Umberger, and G. Umberto Meduri

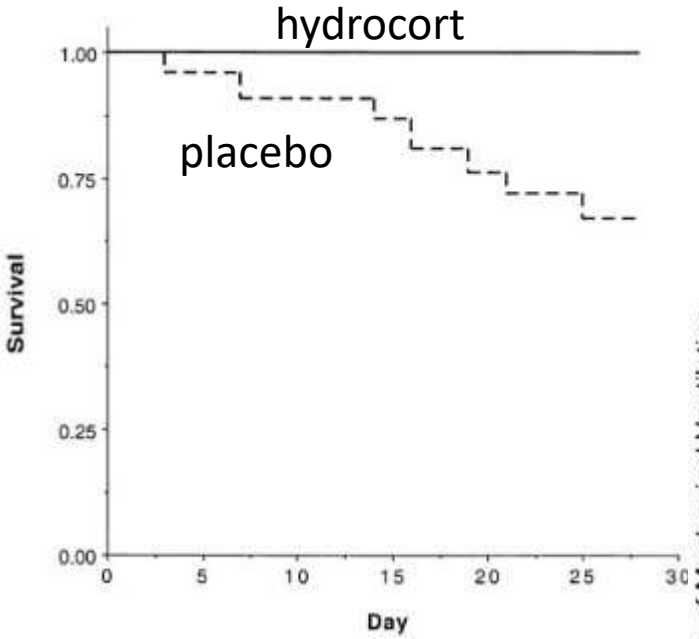
- 46 patients with severe CAP , who were not immune suppressed, no HAP/VAP, disease with corticosteroid requirement >0.5mg/kg/day , GI bleed, isolation of *Candida sp* from multiple sites
- Did not exclude patients on vasopressor requirement (n = 1 vs 2)
- End points : PaO2/FiO2 > 300 or improvement by >100, incidence of septic shock or MODS by day 8 , hospital mortality
- 200 mg hydrocort bolus f/b 10mg/hr x 7 days

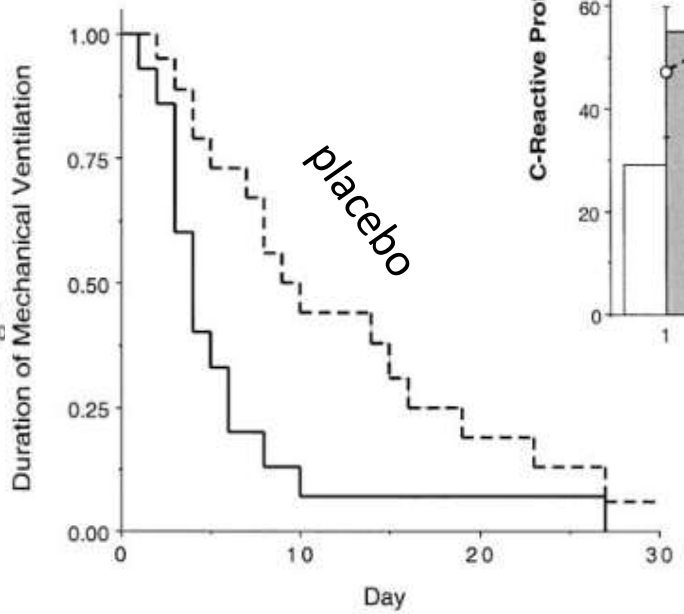
Parameter	Placebo ($n = 23$)	Hydrocortisone ($n = 23$)	p Value
APACHE II score‡‖	18.2 ± 4.0	17.2 ± 4.1	0.39
MODS score‡	1.2 ± 0.4	1.2 ± 0.5	0.75
On mechanical ventilation*	19	15	0.18
$Pa_{O_2}:Fi_{O_2}$‡	178 ± 58	141 ± 49	0.03
$Pa_{O_2}:Fi_{O_2} < 200$‖	13 (57%)	21 (91%)	0.02
Catecholamine-dependent septic shock‖	1 (4%)	2 (9%)	1.0
C-reactive protein, (mg/dl)†**	29 (6–200)	55 (14–349)	0.04
Chest radiograph score‡	2.4 ± 0.6	2.9 ± 0.8	0.03

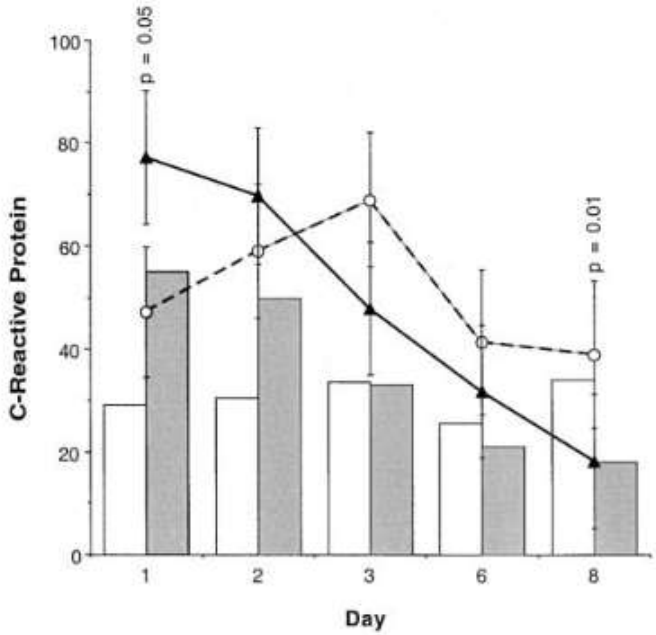
Confalonieri M,et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. http://dx.doi.org/10.1164/rccm.200406-808OC

CLINICAL AND PHYSIOLOGICAL CHARACTERISTICS ON OR BY STUDY DAY 8

Parameter	Placebo ($n = 23$)	Hydrocortisone ($n = 23$)	p Value
On mechanical ventilation *	15 (65%)	6 (26%)	0.008
Mechanical ventilation-free days†‡	0 (0-6)	4 (0-7)	0.01
$Pa_{O_2}:Fi_{O_2}$§	237 ± 92	332 ± 80	0.0008
$Pa_{O_2}:Fi_{O_2} \geq 300$‖	5 (22%)	16 (70%)	0.003
$Pa_{O_2}:Fi_{O_2}$ improvement ≥ 100 from study entry‖	8 (35%)	20 (87%)	0.0007
Chest radiograph score§	2.6 ± 1.3	1.1 ± 0.7	< 0.0001
Improvement in chest radiograph score from Day 1 to Day 8‖	5 (22%)	21 (91%)	< 0.0001
MODS score§	1.0 ± 0.9	0.3 ± 0.5	0.003
Patients with MODS*¶	16 (70%)	8 (35%)	0.02
Delayed septic shock by Day 8‖	9 (43%)	0 (0%)	0.001
New ARDS by Day 8‖	3 (13%)	0 (0%)	0.23
C-reactive protein (mg/dl)†‡**	34 (0–225)	18 (0–44)	0.01
Survival‖	21 (91%)	23 (100%)	0.49







Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial

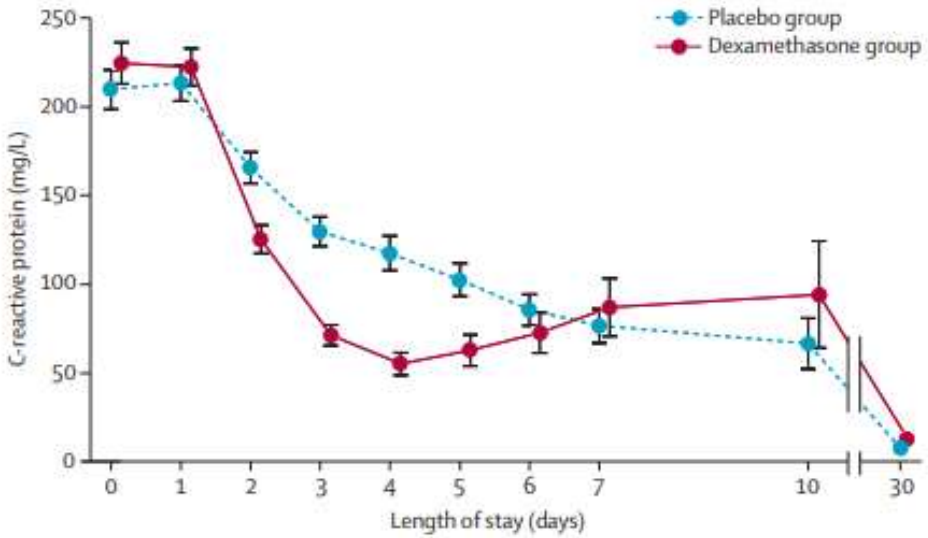
- 304 patients with CAP (non immune suppressed) , CRP >15 mg/L, PSI score of 100 avg , PSI 4/5 (53% vs 42 % in placebo) , 13% COPD
- Could isolate microbe in 55% patients (streptococcus, coxiella, legionella)
- Dexamethasone 5mg OD x 4 days within 12 hrs vs placebo (1st antibiotic)

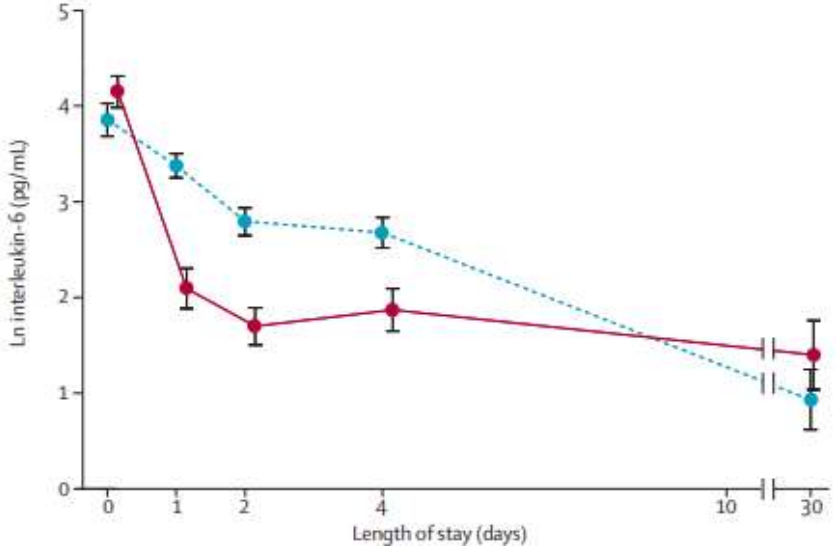
	Dexamethasone group (n=151)	Placebo group (n=153)	p value
Length of stay (days)	6·5 (5·0–9·0)	7·5 (5·3–11·5)	0·0480
In-hospital mortality	8 (5%)	8 (5%)	0·98
Time to death (days)	5·5 (2·6–18·9)	8·8 (3·8–12·8)	0·64
30-day mortality	9 (6%)	11 (7%)	0·68
ICU admission	7 (5%)	10 (7%)	0·47
Time to ICU admission (days)	2·5 (1·5–6·5)	1·8 (1·5–2·6)	0·34
Length of stay in ICU (days)	21·5 (14·5–28·5)	15·5 (10·1–28·5)	0·23
Empyema or pleural effusion	7 (5%)	5 (3%)	0·54
Readmission within 30 days from hospital discharge	7 (5%)	7 (5%)	0·98

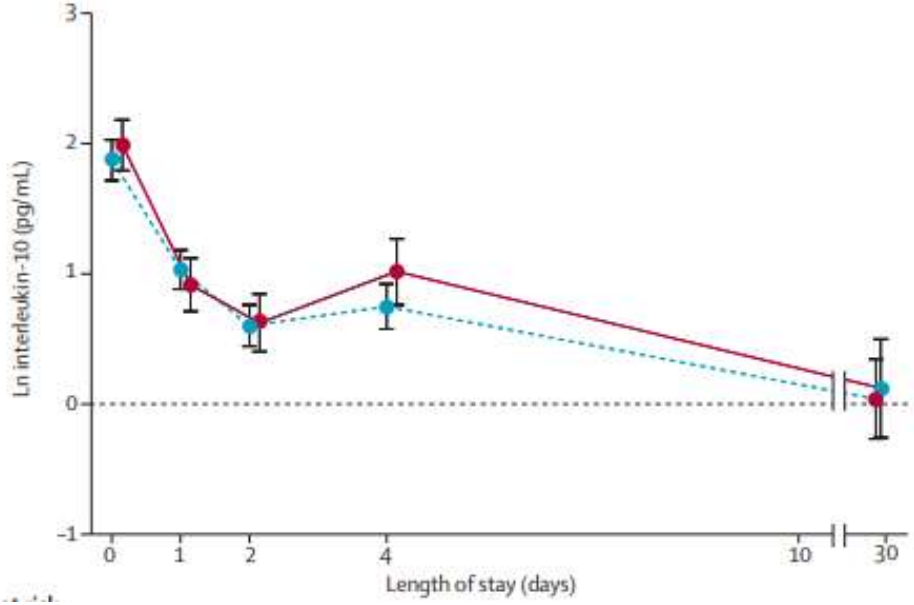
Data are median (IQR) or n (%), unless otherwise stated. ICU=intensive-care unit.

Excluded patients who required direct ICU admission

Meijvis SC, etal., Lancet. 2011 doi: 10.1016/S0140-6736(11)60607-7


Placebo group
Dexamethasone group
C-reactive protein (mg/L)
250
200
150
100
50
0
0
1
2
3
4
5
6
7
10
30
Length of stay (days)


Ln interleukin-6 (pg/mL)
5
4
3
2
1
0
0
1
2
4
10
30
Length of stay (days)


Ln interleukin-10 (pg/mL)
3
2
1
0
−1
0
1
2
4
10
30
Length of stay (days)

Adjunctive treatment with oral dexamethasone in non-ICU patients hospitalised with community-acquired pneumonia: a randomised clinical trial

- 412 Immuno competent patients with CAP (39% severe CAP) were randomized to oral dexamethasone 6mg OD vs placebo for 4 days
- Started steroids within 24 hrs of admission (antibiotics f/b steroids)
- LOS was calculated as 0.5 day, target was that decrease in LOS by 1 day in CAP and 2 days in severe CAP by administration of dexamethasone
- LOS was calculated from admission to discharge/death/ICU shifting
- Active smoker 20-23%, COPD around 20% in each group
- This study terminated early due to slow recruitment (target n-600)

Wittermans 2021 DOI: 10.1183/13993003.02535-2020

TABLE 2 Overview of primary and secondary end-points for the intention-to-treat population

	Dexamethasone[#]	Placebo[¶]	Risk ratio (95% CI)	p-value
Patients	203	198		
Hospital LOS days				
All patients	4.5 (4.0–5.0)	5.0 (4.6–5.4)		0.033[+]
PSI class I–III	4.0 (3.6–4.4)	5.0 (4.5–5.5)		0.065[+]
PSI class IV–V	5.5 (4.6–6.4)	6.0 (5.1–6.9)		0.27[+]
Secondary ICU admission				
All patients	5 (3)	14 (7)	0.35 (0.13–0.95)	0.030[§]
PSI class I–III	0 (0)	6 (5)		0.011[§]
PSI class IV–V	5 (7)	8 (10)	0.64 (0.22–1.87)	0.41[§]
30-day mortality				
All patients	4 (2)	7 (4)	0.56 (0.17–1.87)	0.34[§]
PSI class I–III	1 (1)	2 (2)	0.47 (0.04–5.14)	0.53[§]
PSI class IV–V	3 (4)	5 (6)	0.62 (0.15–2.49)	0.49[§]

In the dexamethasone group hyperglycemia (14 (7%) versus 1 (1%); p=0.001)

Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

- Placebo vs prednisolone 50mg x 7 days in immune-competent CAP patients and time to clinical stability, steroids started within 24 hrs.
- Time to attain stable physiological parameters for >24hrs
- N- 800 : Age 73 yrs, PSI 4/5 (47-52%), COPD in 15-19%, DM in 20%
- Microbiological identification in only 23% of the population (12% streptococcus, 2-4% influenza, 6-7% other viruses)
- Primary endpoint was met with statistically significant decrease in LOS
- Decreased days of antibiotic use , hospital stay at the cost of initial hyperglycemia
- Underpowered to assess mortality difference

blum 2021 lancet doi: 10.1016/S0140-6736(14)62447-8. Epub 2015 Jan 19. PMID: 25608756.

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			HR, OR, or difference (95% CI)	p value
Intention-to-treat: time to clinical stability, days	3·0 (2·5–3·4)	4·4 (4·0–5·0)	HR 1·33 (1·15 to 1·50)	<0·0001
Per-protocol: time to clinical stability, days	3·0 (2·5–3·2)	4·4 (4·0–5·0)	HR 1·35 (1·16 to 1·56)	<0·0001
Recurrent pneumonia	23 (6%)	18 (5%)	OR 1·30 (0·69 to 2·44)	0·42
Re-admission to hospital	32 (9%)	28 (8%)	OR 1·14 (0·67 to 1·93)	0·64
ICU admission	16 (4%)	22 (6%)	OR 0·72 (0·37 to 1·39)	0·32
Death from any cause	16 (4%)	13 (3%)	OR 1·24 (0·59 to 2·62)	0·57

CRP levels lower D3,D5,D7 in prednisolone group, PCT levels not different, data not revealed

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			OR (95% CI) or difference (95% CI)	p value
Incidence of pneumonia-associated complications until day 30				
Complications due to community-acquired pneumonia, any	11 (3%)	22 (6%)	0·49 (0·23 to 1·02)	0·056
Acute respiratory distress syndrome	0	1 (<1%)		
Empyema	1 (0·3%)	5 (1%)		
Respiratory failure, intubation	1 (<1%)	6 (2%)		
Persistence of pneumonia	6 (2%)	5 (1%)		
Mortality associated with community-acquired pneumonia*	5 (1%)	7 (2%)		

Increased incidence of hyperglycemia (19vs 11%) in hospital stay initially had normalised within 1 month after dicsharge

Adjunct prednisone in community-acquired pneumonia: 180-day outcome of a multicentre, double-blind, randomized, placebo-controlled trial

- Outcome until 180 days after adjunct prednisone or placebo in CAP

Endpoints	Placebo ($n = 366$)	Prednisone ($n = 361$)	Adjusted HR or OR (95%CI)[a]	*P* value
Primary endpoint				
Death from any cause – no. (%)	25 (6.8%)	35 (9.7%)	HR 1.15 (0.68–1.95)	0.601
Secondary endpoints				
CAP-related death	7 (1.9%)	6 (1.7%)	OR 0.75 (0.24–2.33)	0.624
Re-Hospitalization – no. (%)	55 (15.0%)	70 (19.4%)	OR 1.33 (0.90–1.96)	0.158
Reason for re-hospitalization – no. (%)				
- Recurrent pneumonia	5 (9%)	21 (30%)		
- Other infection	3 (5.5%)	4 (5.7%)		
- other	41 (74.5%)	39 (55.7%)		
- not reported	6 (11%)	6 (8.6%)		
Recurrent pneumonia – no. (%)	12 (3.3%)	29 (8.0%)	OR 2.57 (1.29–5.12)	0.007
Secondary infections	35 (9.6%)	62 (17.2%)	OR 1.94 (1.25–3.03)	0.003
Type of infection				
- dermatological	1 (3%)	5 (8%)		
- urogenital	10 (29%)	9 (15%)		
- pulmonary	12 (35%)	18 (30%)		
- intestinal	10 (29%)	22 (37%)		
- endocardium or foreign body	1 (3%)	4 (7%)		
- both urogenital and pulmonary	0 (0%)	2 (3%)		
Empyema	7 (1.9%)	3 (0.8%)	OR 0.44 (0.11–1.73)	0.242
New hypertension at day 180	6 (1.6%)	11 (3.0%)	OR 1.90 (0.69–5.18)	0.213
New insulin dependence at day 180	1 (0.3%)	9 (2.5%)	OR 8.73 (1.10–69.62)	0.041

Subgroup analysis for mortality as per PSI, CRP, COPD, Age or microbiological etiology did not reveal any significant difference between the two groups

Blum et al. BMC Pulmonary Medicine (2023) 23:500 https://doi.org/10.1186/s12890-023-02794-w

Confalonieri 2005	**46 severe CAP**	**Hydrocort 10mg/hr infusion for 7 days , trial suspended after interim analysis**	**MODS score 0.3 ± 0.5 in steroids vs 1 ± 0.9 (P=0.003) Delayed shock and mortality improved substantially**	**NNT = 3 to prevent 1 death at D28**
Meijvis 2011	304 CAP	Dexa 5 mg iv bolus for 3 days	Median length of hospital stay decreased by 1 day 6.5 vs 7.5 (P=0.048)	NNT 90 to prevent 1 death at D 30
Blum 2021	785 CAP	Prednisolone 50 mg/ day for 7 days	Median Time to clinical stability 3 days vs 4.4 days (HR 1.33 95% CI 1.15-1.50 P <0.001)	NNH 129 to cause 1 death at 30 days

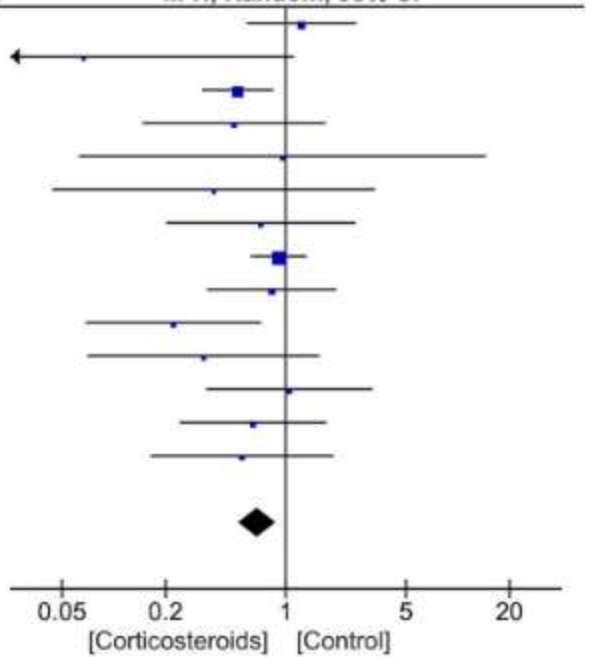
Efficacy and safety of corticosteroids for the treatment of community-acquired pneumonia: A systematic review and meta-analysis of randomized controlled trials

- 15 RCTs (n = 3252), 6 trials hydrocortisone , mortality outcome at 30 days
- + effects on ICU / hospital stay, shock, mechanical ventilation

	Corticosteroids		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Blum 2015	16	392	13	393	10.5%	1.23 [0.60, 2.53]
Confalonieri 2004	0	23	7	23	0.8%	0.07 [0.00, 1.10]
Dequin 2023	25	400	47	395	20.3%	0.53 [0.33, 0.84]
El-Ghamrawy 2006	3	17	6	17	4.1%	0.50 [0.15, 1.68]
Fernández-Serrano 2011	1	23	1	22	0.9%	0.96 [0.06, 14.37]
Marik 1993	1	14	3	16	1.4%	0.38 [0.04, 3.26]
McHardy 1972	3	40	9	86	3.9%	0.72 [0.20, 2.51]
Meduri 2022	47	286	50	277	27.6%	0.91 [0.63, 1.31]
Meijvis 2011	9	151	11	153	7.9%	0.83 [0.35, 1.94]
Nafae 2013	4	60	6	20	4.5%	0.22 [0.07, 0.71]
Sabry 2011	2	40	6	40	2.6%	0.33 [0.07, 1.55]
Snijders 2010	6	104	6	109	5.0%	1.05 [0.35, 3.15]
Torres 2015	6	61	9	59	6.3%	0.64 [0.24, 1.70]
Wittermans 2021	4	203	7	198	4.1%	0.56 [0.17, 1.87]
Total (95% CI)		**1814**		**1808**	**100.0%**	**0.69 [0.53, 0.89]**
Total events	127		181			

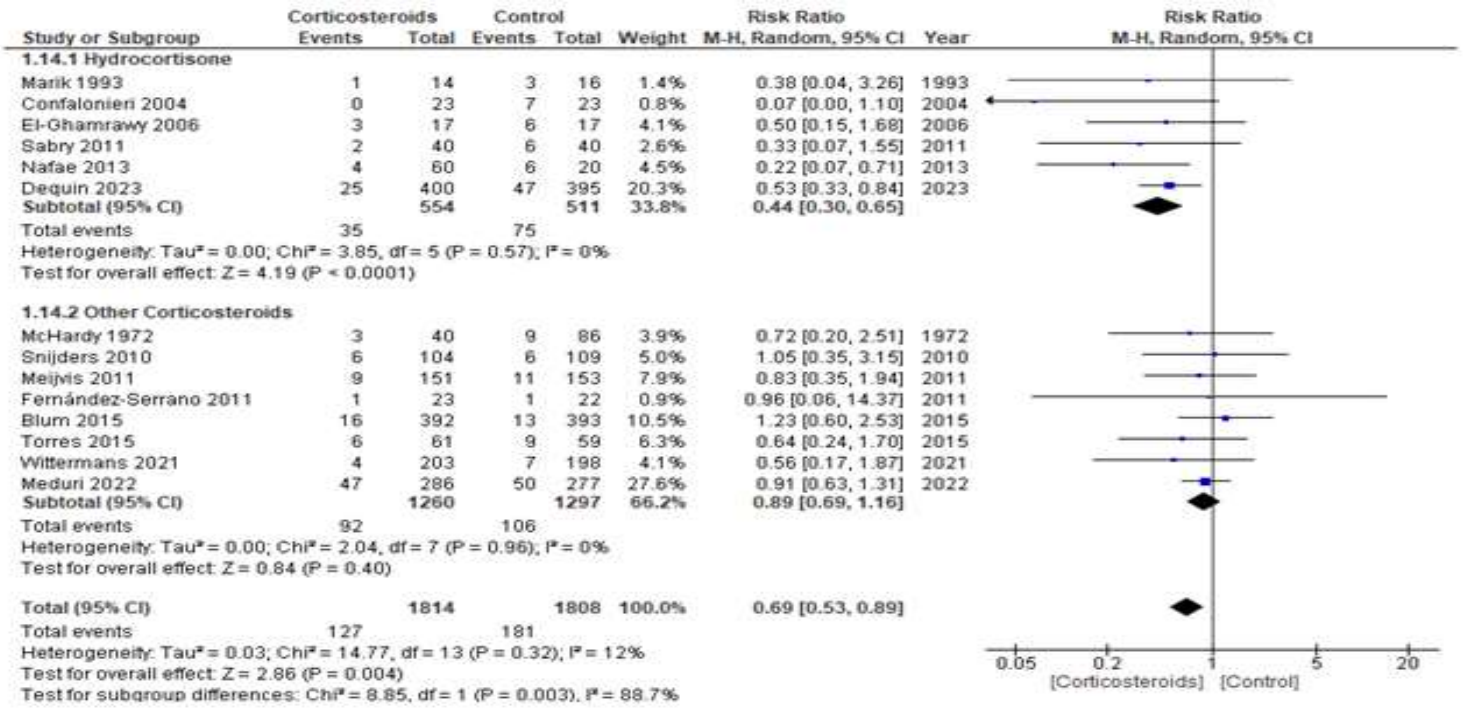
Heterogeneity: Tau² = 0.03; Chi² = 14.77, df = 13 (P = 0.32); I² = 12%

Test for overall effect: Z = 2.86 (P = 0.004)

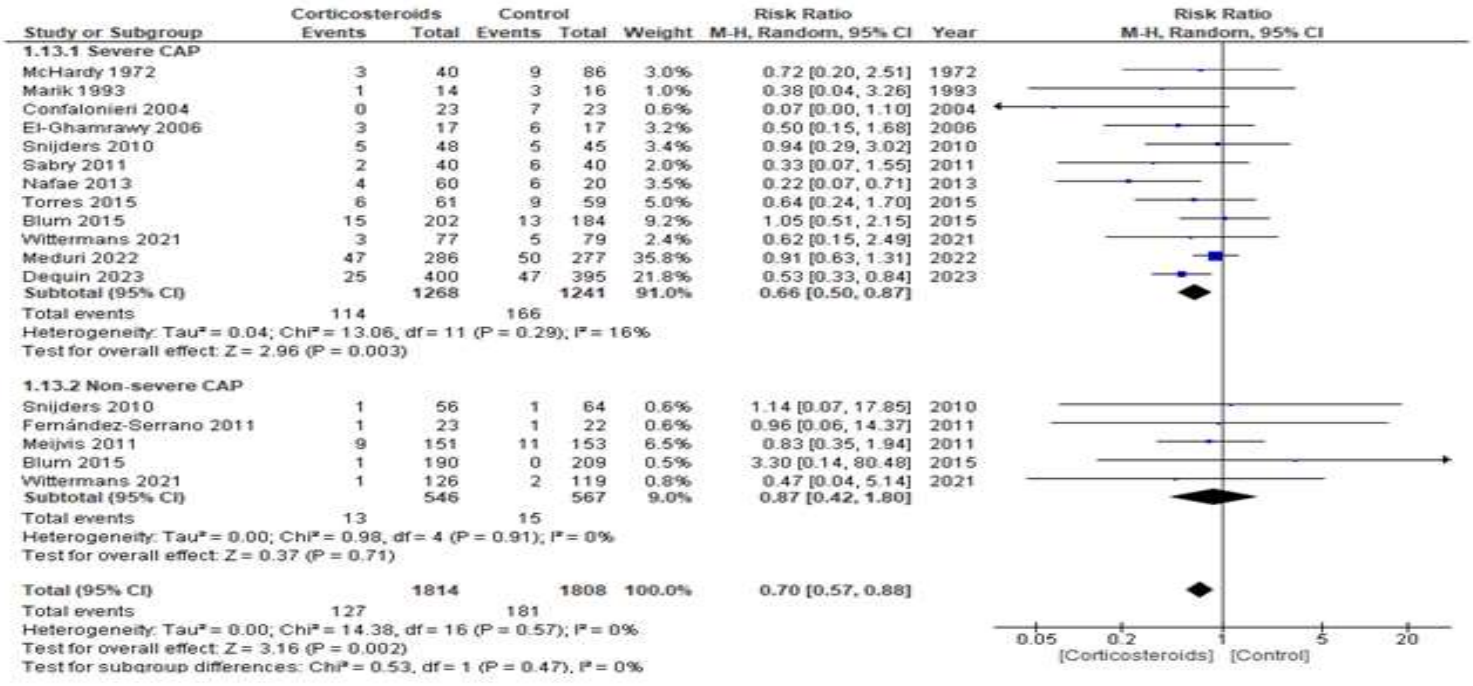


Cheema HA etal., Efficacy and safety of corticosteroids for the treatment of community-acquired pneumonia: A systematic review and meta-analysis of randomized controlled trials. J Crit Care. 2024

Hydrocortisone vs other steroids



Severity of CAP



What the guidelines say

Severe CAP, defined as patient with CAP requiring ICU admission	ERS/ESICM/ESCMID/ALAT 2023 Conditional use *Low evidence*	Multiple regimen accepted (eg, hydrocortisone 200 mg/d within the first 24 h of onset of severe CAP, or IV methylprednisolone equivalent at 40-80 mg/d for 4-7 d)	ICU admission is a subjective and institution-dependent criterion. Guideline recommended low-dose corticosteroids for patients with severe CAP and septic shock but did not provide a recommendation for patients without shock. Hydrocortisone 200 mg/d may be preferred over methylprednisolone 40 mg/d. Guideline was released before publication of the ESCAPe and CAPE COD trials.
Severe CAP, defined as either 1 major criterion or ≥3 minor criteria of the ATS/IDSA CAP severity criteria	ATS/IDSA 2019 Guideline not up to date *Moderate evidence*		Guideline recommends against use of corticosteroids but was released before publication of the ESCAPe and CAPE COD trials and may not apply to severe CAP without shock. Guideline suggested that corticosteroids can be considered for patients with CAP and refractory septic shock.
Severe CAP, no consensus on the definition of severe CAP	SCCM 2024 Strongly recommended *Moderate evidence*		Proposed severity criteria included ATS/IDSA 2007 criteria used in CAPE COD trial, and risk stratification scores.

2024 FOCUSED UPDATE

Society of Critical Care Medicine
The Intensive Care Professionals

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

SYMBOL KEY:

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

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

This infographic visualizes results of a focused update to guidelines previously issued in 2008 and 2017 by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.

Scan or click the QR code to access the 2024 Focused Update Guidelines Executive Summary.

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.*

2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia. Critical Care Medicine 52(5):p e219-e233, May 2024. | DOI: 10.1097/CCM.0000000000006172

Severe community-acquired bacterial pneumonia	Hydrocortisone 200 mg IV once, then 10 mg/hr IV infusion for 7 d ([14], [66]) Hydrocortisone 200 mg IV daily (for 4 or 8 d based on clinical improvement), then taper (for a total duration of 8 or 14 d duration) ([67]) • Hydrocortisone discontinued on ICU discharge Methylprednisolone 0.5 mg/kg IV every 12 hr for 7 d (within 36 hr of hospital admission, C-reactive protein >150 mg/L) ([46]) Methylprednisolone 40 mg IV bolus, then • Days 1–7: 40 mg/d • Days 8–14: 20 mg/d • Days 15–17: 12 mg/d • Days 18–20: 4 mg/d • Administered via continuous infusion in ICU, then changed two divided bid, via IV or enteral, after ICU discharge ([68])

DEXA ARDS

- ARDS with p/f <200, PEEP 10, FiO2 0.5, non immune suppressed
- Dexamethasone 20 x 5days → 10mg x 5 days (<30hrs of onset of ARDS)
- Pneumonia: 50%, Sepsis: 25%, p/f ratio 100-200 in 85% patients
- Ventilator-free days in the dexamethasone group(between-group difference 4·8 days [95% CI 2·57 to 7·03]; p<0·0001)
- ICU mortality 19% vs 31%
- At 60 days, 29 (21%) patients in the dexamethasone group and 50 (36%) patients in the control group had died (between-group difference -15·3% [-25·9 to -4·9]; p=0·0047)
- Hyperglycaemia in the ICU (105 [76%] dexamethasone group vs 97 [70%]

Villar etal., lancet 2020 , https://doi.org/10.1016/s2213-2600(19)30417-5

Carry home message

- Steroids may have some role in CAP, more so in severe CAP
- No evidence to use in immune-compromised, cystic fibrosis, fungal infections , HAP / VAP without certain indications
- Background illness requiring steroids like COPD / auto immune diseases should continue steroids as per recommendations for the underlying co-morbidity
- No evidence / study to classify benefit/harm in terms of bacteria isolated
- There is budding evidence that early steroid use may offer mortality benefit, better treatment response, early weaning, decreased ICU stay and decrease in occurrence of shock / MV

- Little evidence to show increase in side effects except possible hyperglycaemia.
- Increased GI bleed / secondary infections with steroid use is debatable as the results in different trials are conflicting
- Hydrocortisone till now has an upper edge vs other steroids for the desired results
- Preferable to use longer duration of steroids (- 7 days)
- No clear biomarker has been still found to be helpful to select intervention
- Exact group of patients in which it will be helpful needs more studies

How can we use it

- Adult patient
- Severe CAP (PSI 4/5, CURB 65 > 3 , ATS IDSA)
- ICU admission
- Early antibiotic followed by steroids, preferable within 1st 24 hrs
- Hydrocortisone for > 7 days
- Definitely not to use in patients who are immune suppressed , risk of fungal pneumonia , influenza , TB , HAP / VAP
- Definitely use in septic shock patients with our same protocol