Corticosteroids for severe community-acquired pneumonia

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IHU PROMETHEUS

FHU SEPSIS
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Context

Lower respiratory tract infections associated with a considerable health, social and economic burden

4th global cause of death
2% of all deaths in USA
8 -25% ICU admission
22% 6-m readmission

£731 million/year (UK)
16 k€/hosp (France)
55 k$ (USA)

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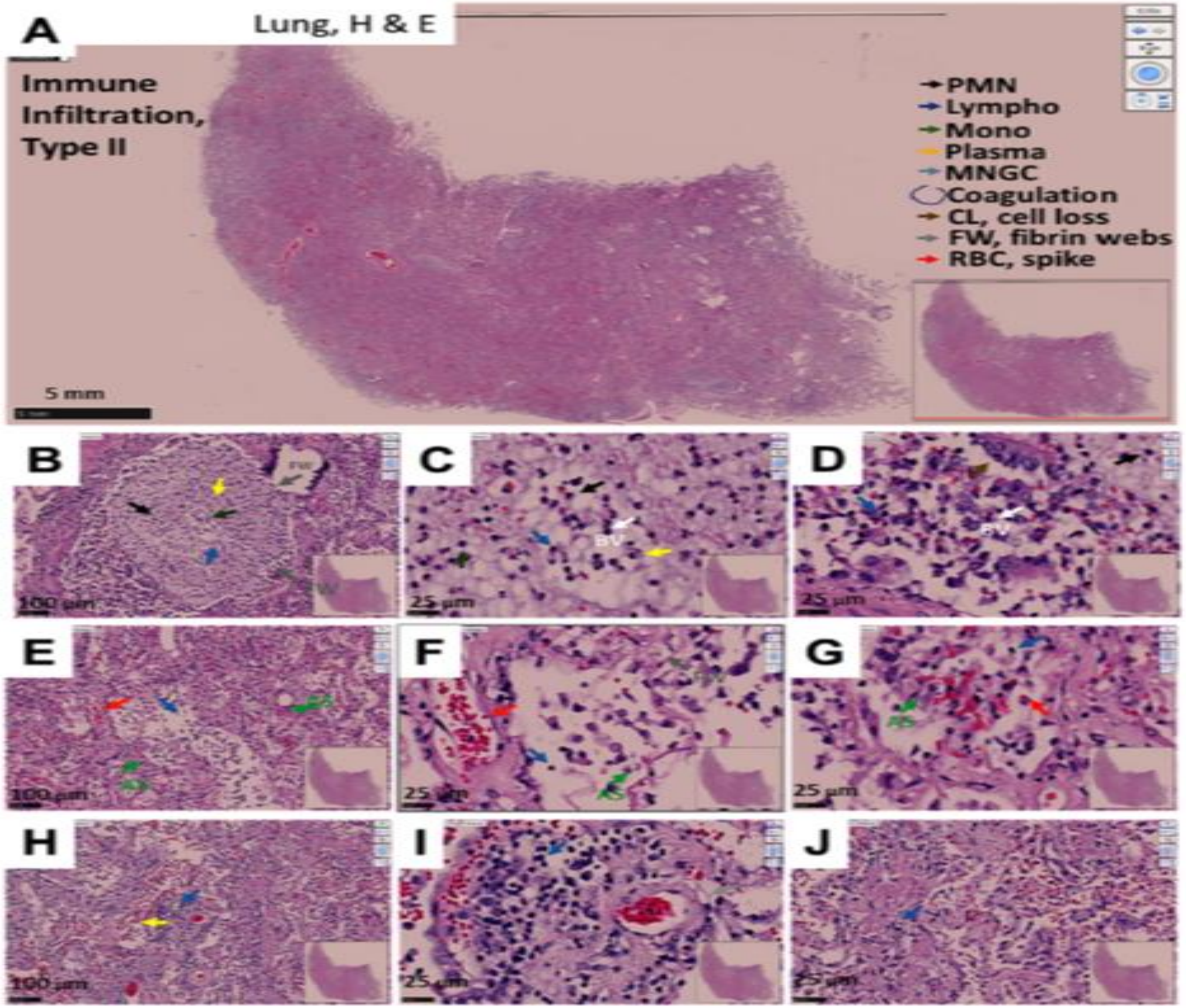
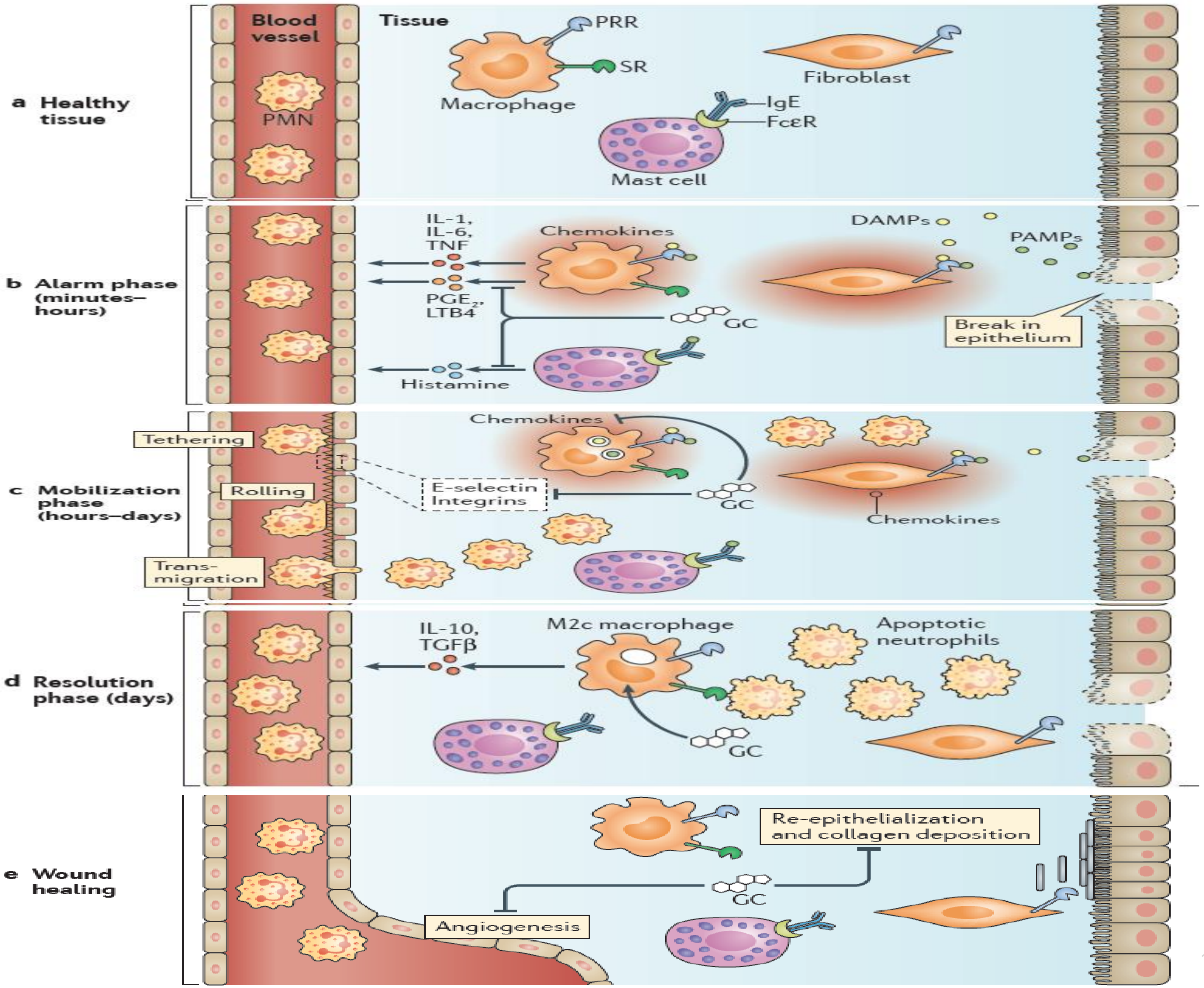
Rational

45 years old
Pneumococcal CAP
Died D-7





Nature Rev Immunol 2017

Clinical evidence

JCI The Journal of Clinical Investigation

EFFECT OF CORTISONE ON ACUTE STREPTOCOCCAL INFECTIONS AND POST-STREPTOCOCCAL COMPLICATIONS

Edward O. Hahn, … , Floyd W. Denny, Lewis W. Wannamaker

J Clin Invest. 1951;30(3):274-281. https://doi.org/10.1172/JCI102441.

Research Article

TABLE I

Comparability of the 87 cases in each of the treated and control groups

	Cortisone group *per cent*	Control group *per cent*
History of tonsillectomy	26.4	31.0
Age 17–21	77.0	74.7
*Symptoms:**		
Chilliness	65.5	75.8
Feverishness	82.7	86.2
Malaise	41.3	56.3
Sore Throat	82.7	85.0
Headache	86.2	80.4
Physical signs:†		
Enlarged or tender cervical nodes	91.8	90.8
Lymphoid hyperplasia	37.9	37.9
Laboratory:		
Group A streptococci on admission	89.7	88.5
Type 14	54.0	65.5
Type 24	17.2	10.3
Type 6	9.1	9.1
Leucocyte count 12,000 or greater	91.9	86.2
Antistreptolysin titer—125 units or less on admission	68.9	67.8

* Symptoms occurring during first 12 hours of illness.
† Physical signs present on admission examination.

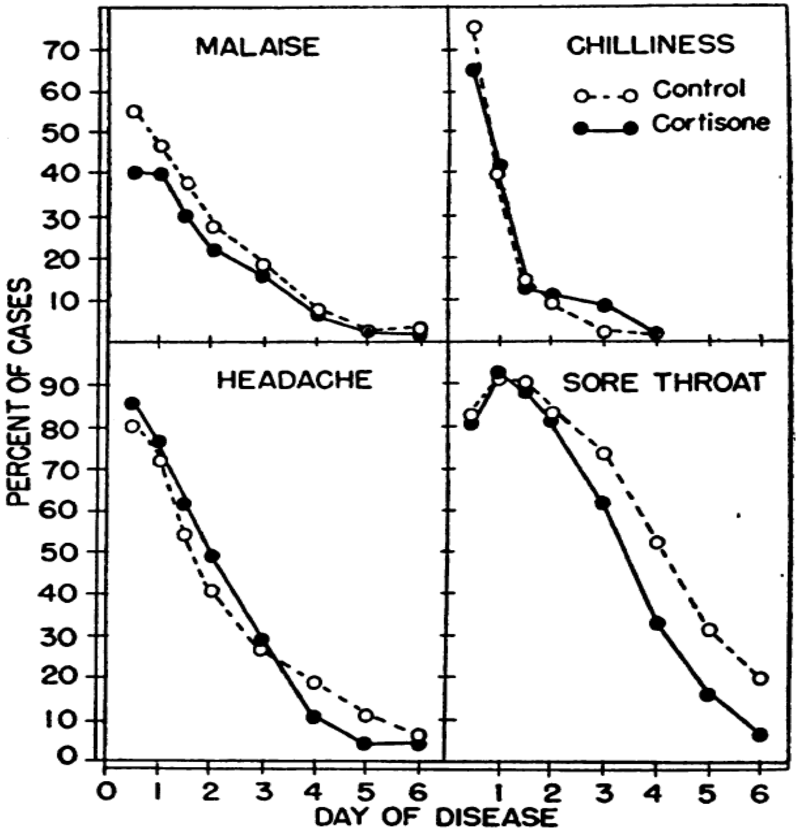


Fig. 1. Effect of Cortisone Therapy on the Symptoms of Streptococcal Tonsillitis and Pharyngitis

TABLE II

The effect of cortisone on the complications of streptococcal sore throat

Complication	Cortisone group (87 cases)	Control group (87 cases)
Suppurative:		
A. During treatment		
1. Peritonsillar cellulitis	0	3
2. Otitis media	4	7
3. Appendicitis	1	0
B. Following treatment		
1. Exudative tonsillitis	4	3
2. Peritonsillar cellulitis	1	2
3. Otitis media	1	0
Non-suppurative:		
Rheumatic fever	2	5

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY MAY 2019 AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA AUGUST 2019

Table 2. Differences between the 2019 and 2007 American Thoracic Society/Infectious Diseases Society of America Community-acquired Pneumonia Guidelines

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *Pseudomonas aeruginosa*
Blood culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *P. aeruginosa*
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or *P. aeruginosa* coverage. Increased emphasis on deescalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-Lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*.

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Clinical evidence

What’s new?

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

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, B. Souweine, G. Voiriot, G. Colin, J.-P. Frat, J.-P. Mira, N. Barbarot, B. François, G. Louis, S. Gibot, C. Guitton, C. Giacardi, S. Hraiech, S. Vimeux, E. L'Her, H. Faure, J.-E. Herbrecht, C. Bouisse, A. Joret, N. Terzi, A. Gacouin, C. Quentin, M. Jourdain, M. Leclerc, C. Coffre, H. Bourgoin, C. Lengellé, C. Caille-Fénérol, B. Giraudeau, and A. Le Gouge, for the CRICS-TriGGERSep Network*

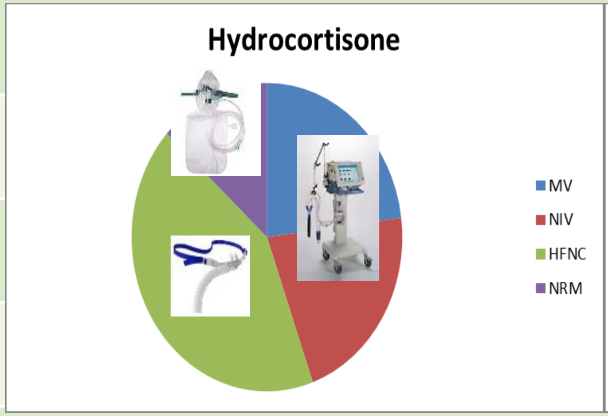
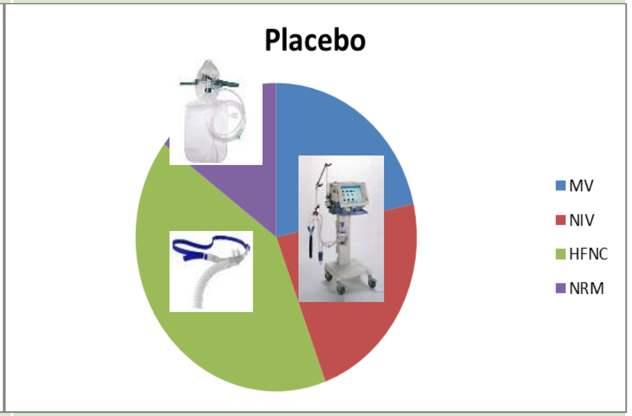
CAPE COD trial

- Community-Acquired Pneumonia: Evaluation of COrticosteroiDs
- Investigator-initiated, blinded randomized controlled trial

- Aim

To determine whether the early administration of hydrocortisone compared to placebo improved mortality in patients with community acquired pneumonia admitted to the ICU

Baseline characteristics

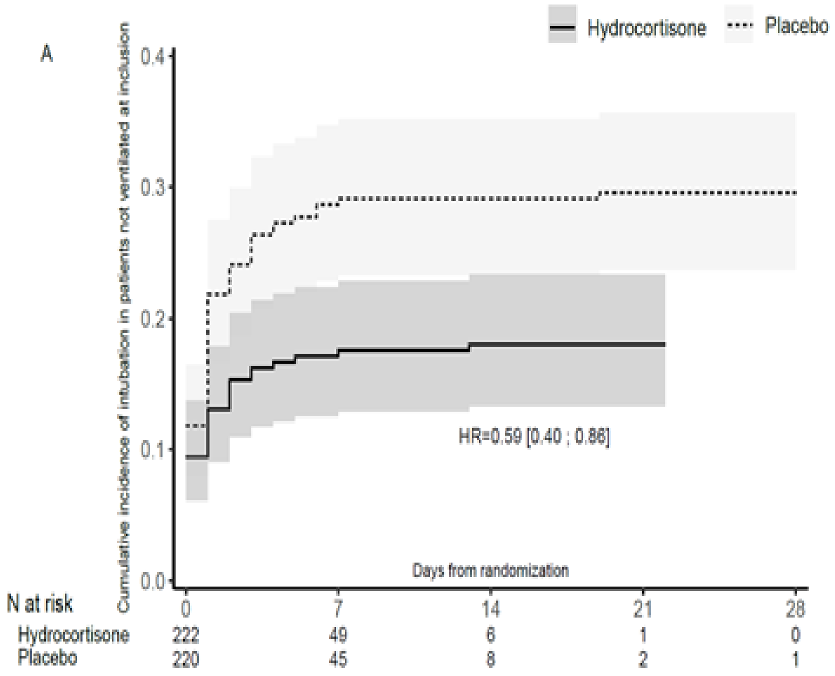
	HC (n=400)	Placebo (n=395)
Age, median (IQR), y	67 (58;77)	67 (58;78)
Male/Female, %	70.3/29.7	68.3/31.4
Respiratory support		
PaO_2/FiO_2, median (IQR)	143 (104;195)	137 (96;192)
SAPS II, median (IQR)	37 (30;45)	38 (31;47)
SOFA, median (IQR)	4 (3;6)	4 (3;6)

Results: mortality

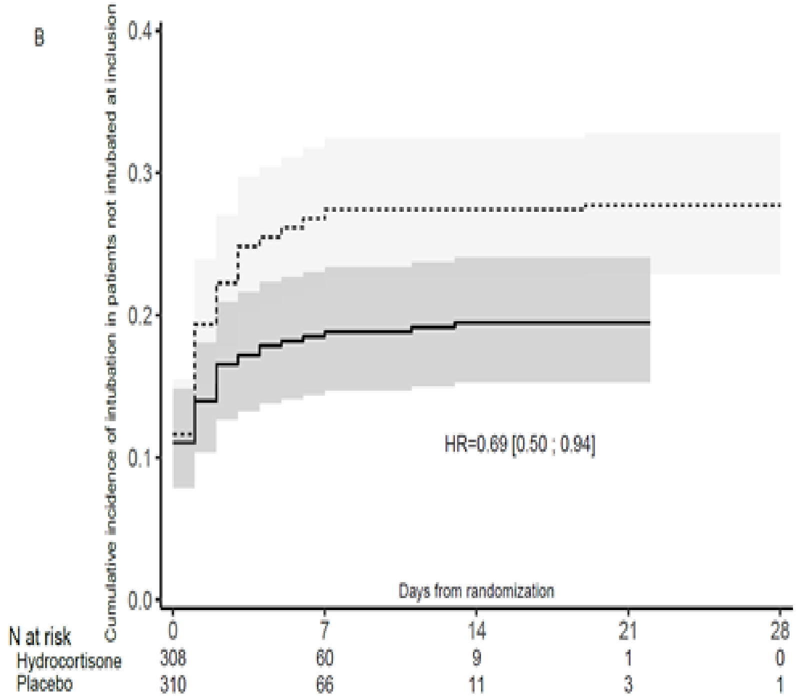
	HC (n=400)	Placebo (n=395)	Difference	P
Death D28	6.3% [3.9;8.6]	11.9% [8.7;15.1]	-5.6 [-9.6;-1.7]	0.0055
Death D90	9.3% [6.4;12.2]	14.7% [11.1;18.2]	-5.4 [-9.9;-0.8]	0.02

Cumulative incidence of intubation

Among 442 non NM patients

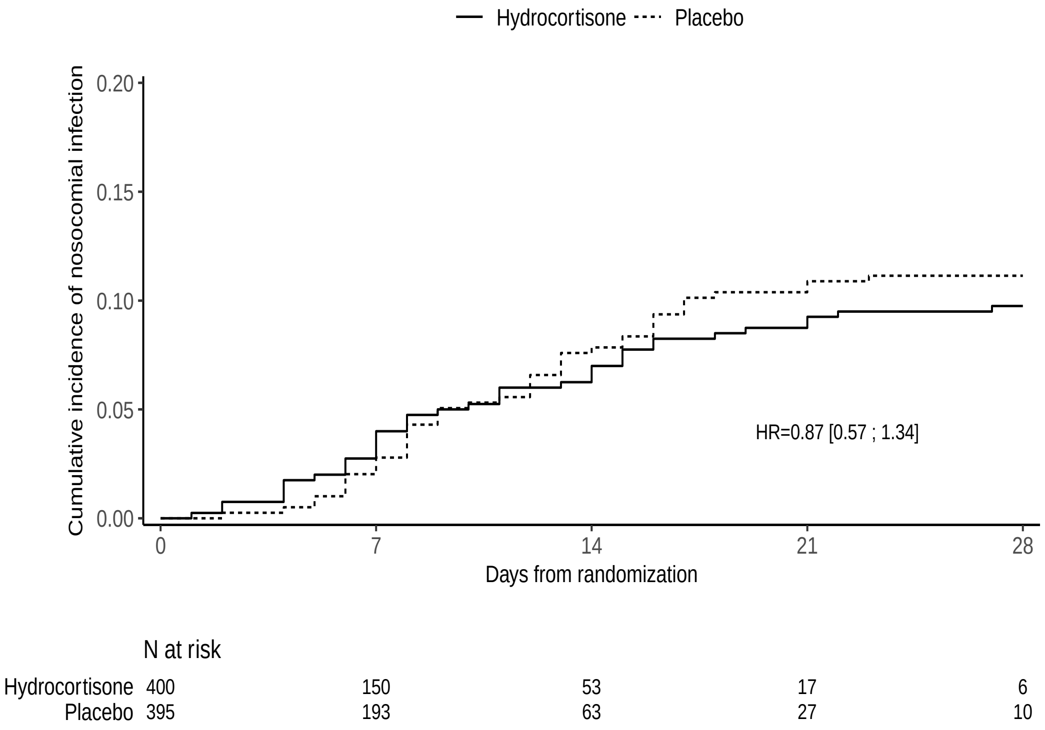


Among 618 non IMV patients



Safety

Cumulative incidence of hospital-acquired infection

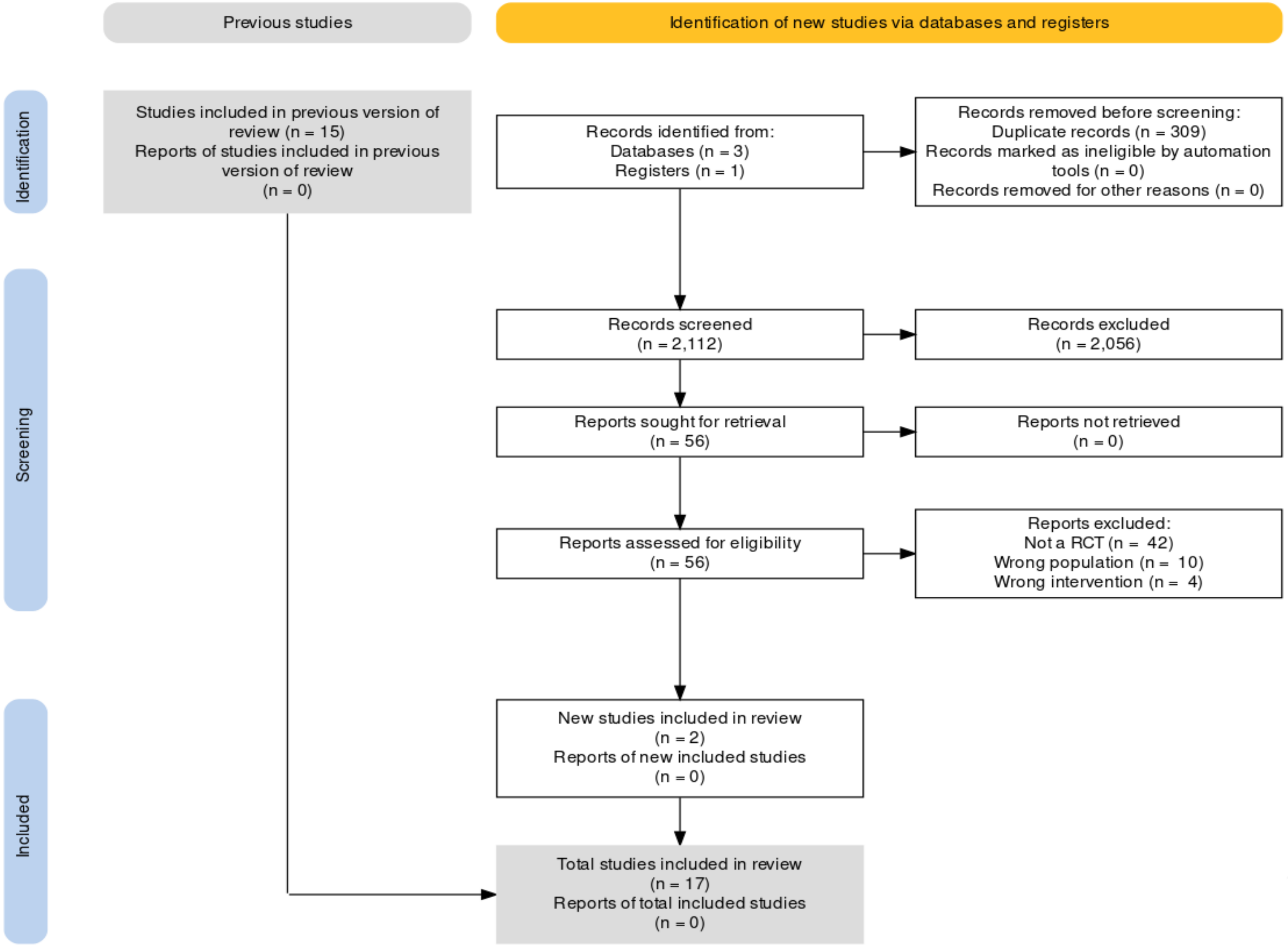


Daily dose of insulin, from inclusion to D7

Median (IQR), IU/day

HC (n=400)	Placebo (n=395)	P
35.5 [15 ; 57.5]	20.5 [9.4;48.5]	0.0002

Corticosteroids in CAP : A SR, pairwise and dose response meta-analysis



Pitre for SCCM CIRCI TF, 2023

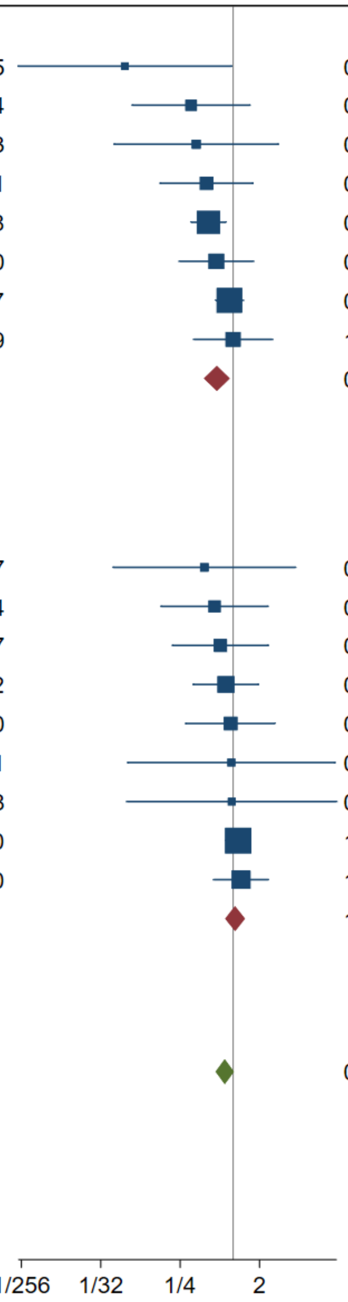
Study	1) Bias arising from the randomization process	2) Bias due to deviations from the intended intervention	3) Bias due to missing outcome data	4) Bias in measurement of the outcome	5) Bias in selection of the reported results
Confalonieri et al. 2005	Low	Low	Low	Low	Low
El-Ghamrawy et al. 2006	Probably high	Probably high	Low	Low	Low
ESCAPe	Low	Low	Low	Low	Low
Fernández Serrano et al. 2011	Probably low	Low	Low	Low	Probably high
Gang et al. 2016	High	High	Probably high	Probably low	Probably high
IMPRoVE-GAP	Probably high	Probably high	Probably high	Low	Low
Marik et al. 1993	Probably high	Probably high	Low	Low	Probably high
McHardy and Schonell et al. 1972	High	High	Low	Low	Probably high
Nafae et al. 2013	Probably high	High	Low	Probably low	Probably low
Ovidius	Low	Low	Low	Low	Low
Sabry et al. 2011	Probably low	Low	Low	Low	Probably low
Snijders et al. 2010	Probably low	Low	Low	Low	Probably low
STEP	Low	Low	Low	Low	Low
Torres et al. 2015	Low	Low	Low	Low	Low
Wagner et al. 1956	Probably high	Probably high	Low	Low	Low
Wittermans et al. 2021	Low	Low	Low	Low	Low

Legend

- Low
- Probably low
- Probably high
- High

Mortality

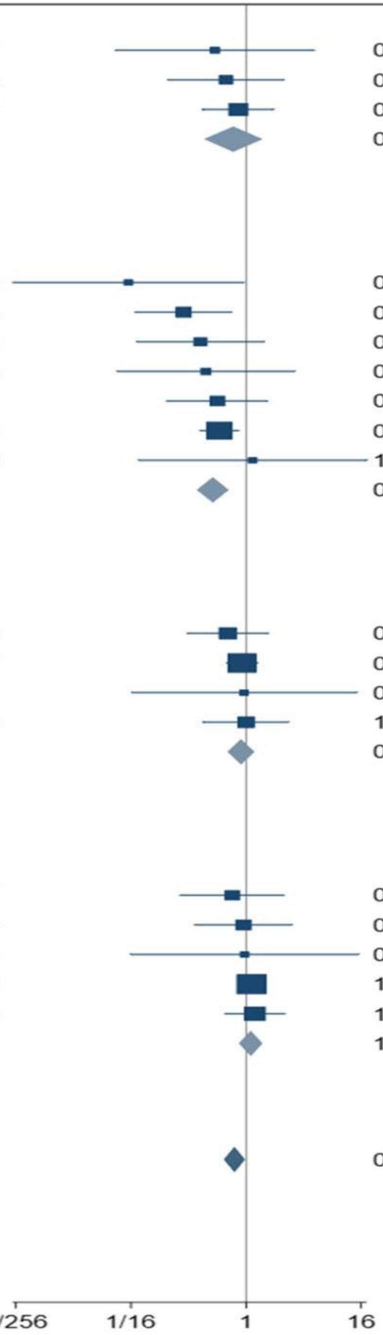
Study	Corticosteroids Yes	Corticosteroids No	Usual care Yes	Usual care No	Risk ratio with 95% CI	Weight (%)
ICU						
Confalonieri et al. 2005	0	23	8	15	0.06 [0.00, 0.96]	0.79
Sabry et al. 2011	2	38	6	34	0.33 [0.07, 1.55]	2.43
Marik et al. 1993	1	13	3	13	0.38 [0.04, 3.26]	1.31
El-Ghamrawy et al. 2006	3	14	6	11	0.50 [0.15, 1.68]	3.71
CAPE COD	25	375	47	348	0.53 [0.33, 0.84]	13.81
Torres et al. 2015	6	55	9	50	0.64 [0.24, 1.70]	5.37
ESCAPe	47	250	50	237	0.91 [0.63, 1.31]	16.88
Gang et al. 2016	6	29	6	29	1.00 [0.36, 2.80]	4.87
Heterogeneity: $\tau^2 = 0.05$, $I^2 = 21.37\%$, $H^2 = 1.27$					0.65 [0.47, 0.92]	
Test of $\theta_i = \theta_j$: Q(7) = 8.44, p = 0.30						
Test of $\theta = 0$: z = -2.47, p = 0.01						
Non-ICU						
Wittermans* et al. 2021	1	125	2	117	0.47 [0.04, 5.14]	1.07
Wittermans et al. 2021	3	74	5	74	0.62 [0.15, 2.49]	2.89
McHardy and Schonell et al. 1972	3	37	9	77	0.72 [0.20, 2.51]	3.51
Meijvis et al. 2011	9	142	11	142	0.83 [0.35, 1.94]	6.55
Snijders et al. 2010	5	43	5	40	0.94 [0.29, 3.02]	3.93
Fernández Serrano et al. 2011	1	22	1	21	0.96 [0.06, 14.37]	0.84
Snijders* et al. 2010	1	60	1	58	0.97 [0.06, 15.11]	0.81
IMPROVe-GAP	63	301	57	320	1.14 [0.82, 1.59]	18.06
STEP	16	376	13	380	1.23 [0.60, 2.53]	8.36
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					1.05 [0.81, 1.36]	
Test of $\theta_i = \theta_j$: Q(8) = 2.15, p = 0.98						
Test of $\theta = 0$: z = 0.38, p = 0.70						
Overall					0.80 [0.63, 1.02]	
Heterogeneity: $\tau^2 = 0.04$, $I^2 = 20.27\%$, $H^2 = 1.25$						
Test of $\theta_i = \theta_j$: Q(16) = 15.61, p = 0.48						
Test of $\theta = 0$: z = -1.80, p = 0.07						
Test of group differences: $Q_b(1) = 4.81$, p = 0.03						



Random-effects REML model

Pitre for SCCM CIRCI TF, 2023

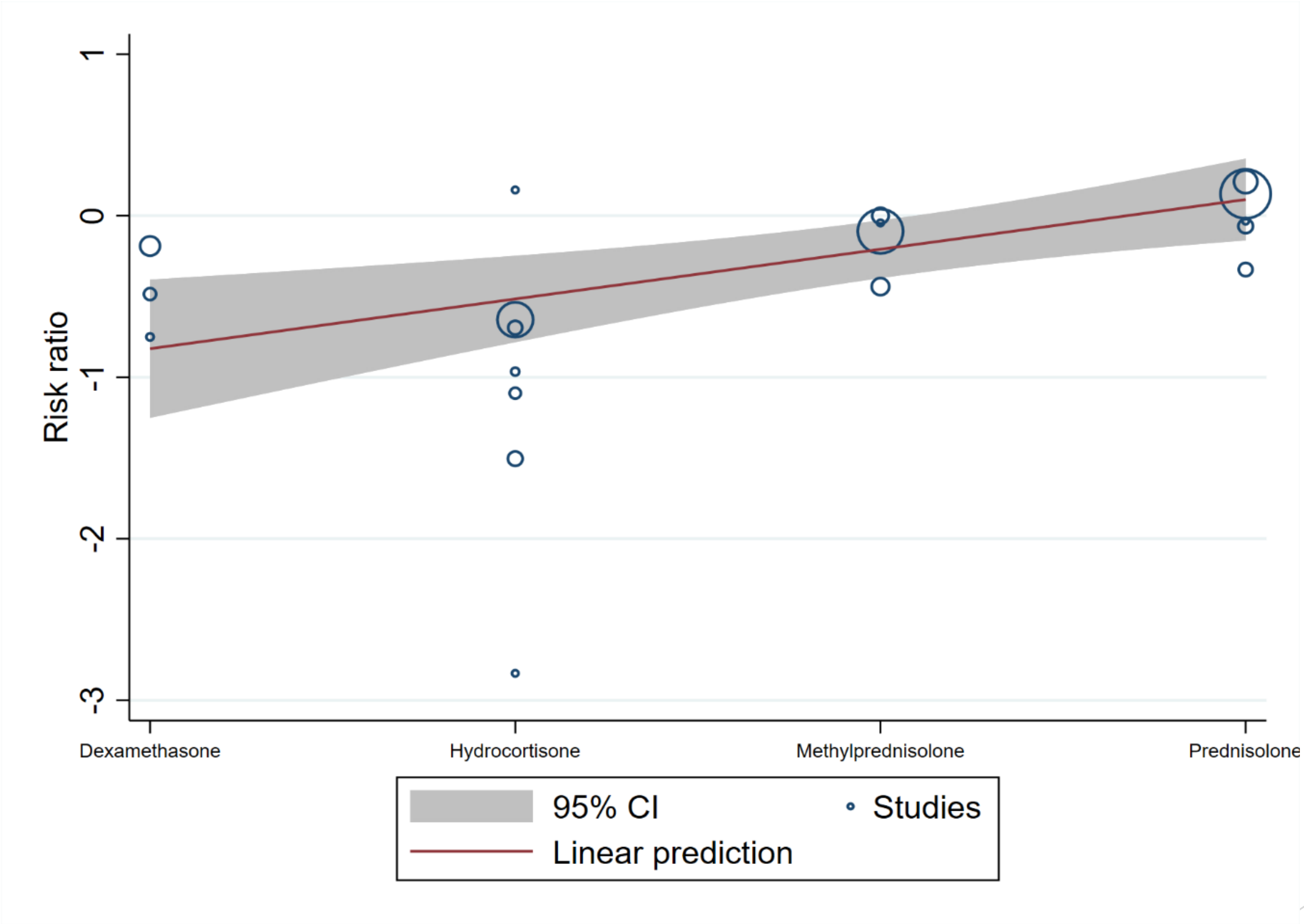
Study	Corticosteroids Yes	Corticosteroids No	Usual care Yes	Usual care No	Risk ratio with 95% CI	Weight (%)
Dexamethasone						
Wittermans* et al. 2021	1	125	2	117	0.47 [0.04, 5.14]	1.07
Wittermans et al. 2021	3	74	5	74	0.62 [0.15, 2.49]	2.89
Meijvis et al. 2011	9	142	11	142	0.83 [0.35, 1.94]	6.55
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					0.73 [0.37, 1.47]	
Test of $\theta_i = \theta_j$: Q(2) = 0.27, p = 0.87						
Test of $\theta = 0$: z = -0.87, p = 0.38						
Hydrocortisone						
Confalonieri et al. 2005	0	23	8	15	0.06 [0.00, 0.96]	0.79
Nafae et al. 2013	4	56	6	14	0.22 [0.07, 0.71]	4.00
Sabry et al. 2011	2	38	6	34	0.33 [0.07, 1.55]	2.43
Marik et al. 1993	1	13	3	13	0.38 [0.04, 3.26]	1.31
El-Ghamrawy et al. 2006	3	14	6	11	0.50 [0.15, 1.68]	3.71
CAPE COD	25	375	47	348	0.53 [0.33, 0.84]	13.81
Wagner et a. 1956	1	51	1	60	1.17 [0.08, 18.30]	0.82
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					0.45 [0.31, 0.65]	
Test of $\theta_i = \theta_j$: Q(6) = 4.55, p = 0.60						
Test of $\theta = 0$: z = -4.15, p = 0.00						
Methylprednisolone						
Torres et al. 2015	6	55	9	50	0.64 [0.24, 1.70]	5.37
ESCAPe	47	250	50	237	0.91 [0.63, 1.31]	16.88
Fernández Serrano et al. 2011	1	22	1	21	0.96 [0.06, 14.37]	0.84
Gang et al. 2016	6	29	6	29	1.00 [0.36, 2.80]	4.87
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					0.88 [0.64, 1.22]	
Test of $\theta_i = \theta_j$: Q(3) = 0.49, p = 0.92						
Test of $\theta = 0$: z = -0.76, p = 0.45						
Prednisolone						
McHardy and Schonell et al. 1972	3	37	9	77	0.72 [0.20, 2.51]	3.51
Snijders et al. 2010	5	43	5	40	0.94 [0.29, 3.02]	3.93
Snijders* et al. 2010	1	60	1	58	0.97 [0.06, 15.11]	0.81
IMPROVe-GAP	63	301	57	320	1.14 [0.82, 1.59]	18.06
STEP	16	376	13	380	1.23 [0.60, 2.53]	8.36
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					1.12 [0.84, 1.48]	
Test of $\theta_i = \theta_j$: Q(4) = 0.67, p = 0.95						
Test of $\theta = 0$: z = 0.77, p = 0.44						
Overall					0.75 [0.59, 0.97]	
Heterogeneity: $\tau^2 = 0.06$, $I^2 = 25.97\%$, $H^2 = 1.35$						
Test of $\theta_i = \theta_j$: Q(18) = 20.70, p = 0.29						
Test of $\theta = 0$: z = -2.19, p = 0.03						
Test of group differences: $Q_b(3) = 14.72$, p = 0.00						



Random-effects REML model

Pitre for SCCM CIRCI TF, 2023

Mortality/corticosteroid type meta-regression (p=0.001)



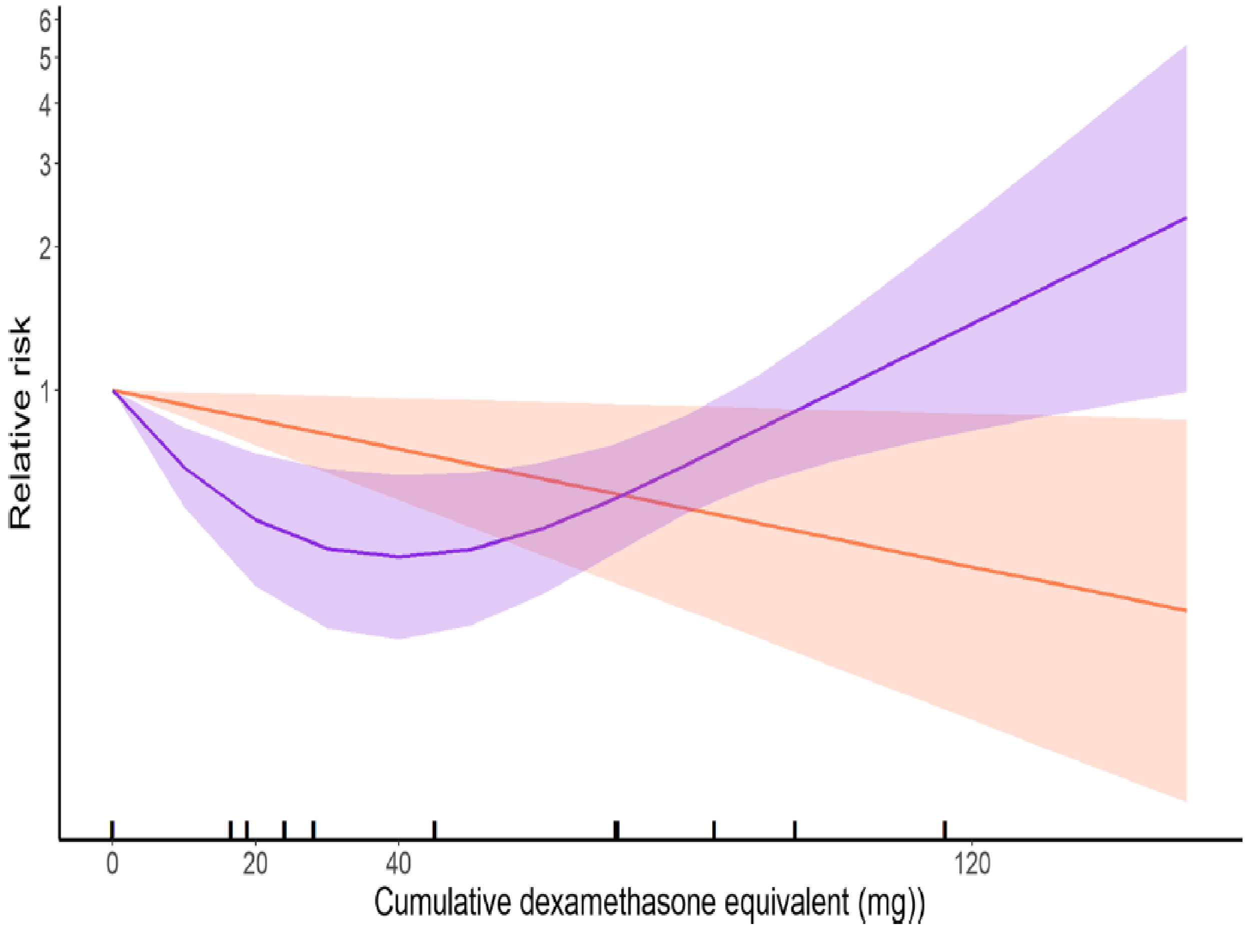
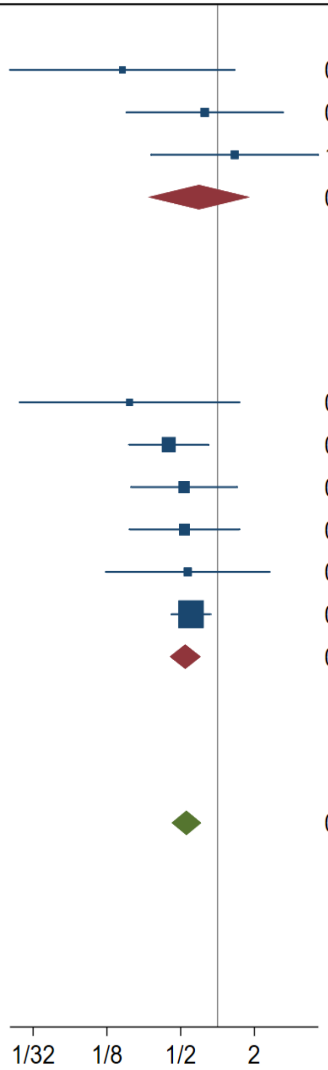


Figure 4 Dose-response curve. The curved purple line represents the non-linear dose-response relationship, and the purple ribbons represent 95% confidence intervals (95% CI). The yellow linear line represents the linear dose-response relationship, and the ribbons represent 95% CI.

Pitre for SCCM CIRCI TF, 2023

Need for IMV

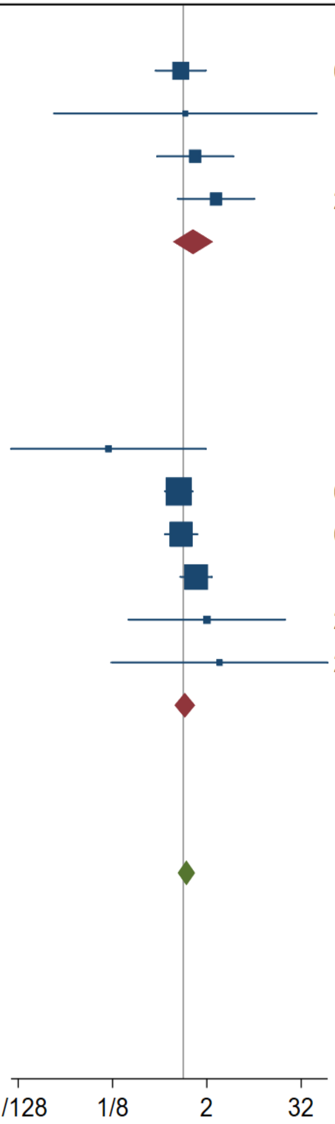
Study	Corticosteroids Yes	Corticosteroids No	Usual care Yes	Usual care No	Risk ratio with 95% CI	Weight (%)
Less severe						
STEP	1	391	6	387	0.17 [0.02, 1.38]	1.75
Snijders et al. 2010	3	101	4	105	0.79 [0.18, 3.43]	3.59
IMPROVe-GAP	4	360	3	374	1.38 [0.29, 6.65]	3.16
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					0.70 [0.27, 1.84]	
Test of $\theta_i = \theta_j$: Q(2) = 2.51, p = 0.29						
Test of $\theta = 0$: z = -0.72, p = 0.47						
More severe						
Fernández Serrano et al. 2011	1	22	5	17	0.19 [0.02, 1.51]	1.83
Confalonieri et al. 2005	6	17	15	8	0.40 [0.19, 0.85]	13.86
Nafae et al. 2013	8	52	5	15	0.53 [0.20, 1.44]	7.85
Torres et al. 2015	5	56	9	50	0.54 [0.19, 1.51]	7.30
Marik et al. 1993	2	12	4	12	0.57 [0.12, 2.66]	3.29
CAPE COD	40	360	65	330	0.61 [0.42, 0.88]	57.37
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					0.54 [0.41, 0.73]	
Test of $\theta_i = \theta_j$: Q(5) = 1.98, p = 0.85						
Test of $\theta = 0$: z = -4.08, p = 0.00						
Overall					0.56 [0.42, 0.74]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						
Test of $\theta_i = \theta_j$: Q(8) = 4.75, p = 0.78						
Test of $\theta = 0$: z = -4.11, p = 0.00						
Test of group differences: $Q_b(1) = 0.26$, p = 0.61						



Random-effects REML model

Risk for secondary Infections

Study	Corticosteroids Yes	Corticosteroids No	Usual care Yes	Usual care No	Risk ratio with 95% CI	Weight (%)
Less severe						
STEP	13	379	14	379	0.93 [0.44, 1.95]	10.66
Mikami et al. 2007	0	15	0	16	1.06 [0.02, 50.43]	0.43
Meijvis et al. 2011	7	144	5	148	1.42 [0.46, 4.37]	4.85
Snijders et al. 2010	10	94	4	105	2.62 [0.85, 8.09]	4.83
Heterogeneity: $\tau^2 = 0.04$, $I^2 = 10.22\%$, $H^2 = 1.11$					1.33 [0.74, 2.40]	
Test of $\theta_i = \theta_j$: Q(3) = 2.30, p = 0.51						
Test of $\theta = 0$: z = 0.95, p = 0.34						
More severe						
Confalonieri et al. 2005	0	23	4	19	0.11 [0.01, 1.95]	0.77
CAPE COD	39	361	44	351	0.88 [0.58, 1.32]	29.74
Gang et al. 2016	15	14	16	13	0.94 [0.58, 1.52]	22.84
ESCAPe	38	249	27	270	1.46 [0.91, 2.32]	24.07
El-Ghamrawy et al. 2006	2	15	1	16	2.00 [0.20, 20.04]	1.19
Torres et al. 2015	1	60	0	59	2.90 [0.12, 69.87]	0.63
Heterogeneity: $\tau^2 = 0.02$, $I^2 = 14.51\%$, $H^2 = 1.17$					1.05 [0.77, 1.41]	
Test of $\theta_i = \theta_j$: Q(5) = 5.92, p = 0.31						
Test of $\theta = 0$: z = 0.29, p = 0.77						
Overall					1.09 [0.85, 1.41]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 7.16\%$, $H^2 = 1.08$						
Test of $\theta_i = \theta_j$: Q(9) = 8.75, p = 0.46						
Test of $\theta = 0$: z = 0.70, p = 0.48						
Test of group differences: $Q_b(1) = 0.51$, p = 0.47						



Random-effects REML model

Conclusions

- Corticosteroids probably improve short and mid-term all-cause mortality in adults with CAP
- Corticosteroids effects on mortality are probably more marked in ICU patients with CAP
- Corticosteroids probably hasten clinical cure, resolution of shock, respiratory failure and of multiple organ failures, and prevent ICU admission