Corticosteroids for community-acquired pneumonia

Djillali ANNANE, Raymond Poincaré Hospital,

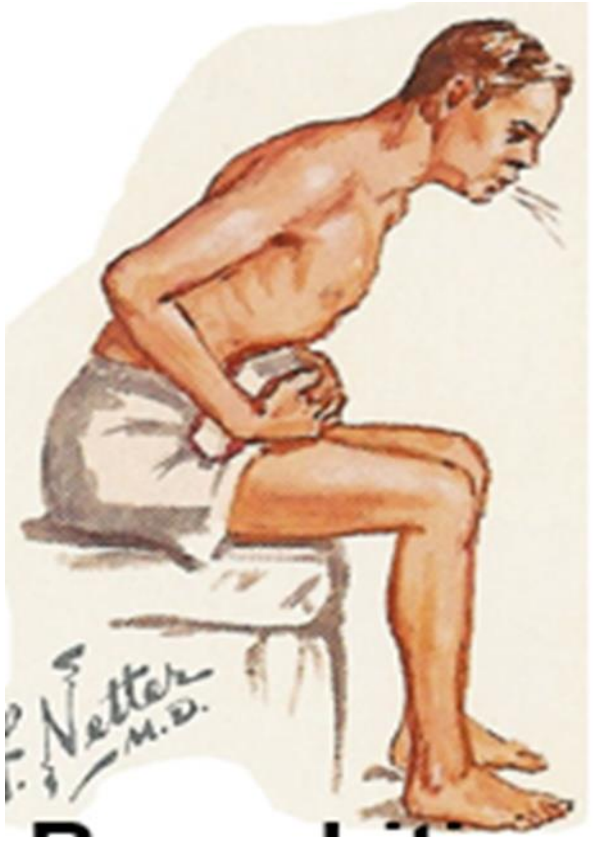
University Paris Saclay-UVSQ, Garches, France

IHU PROMETHEUS

Conflict of Interest

- Financial:
  - since 1995 I have received multiple grants from French ministry of health, French ministry of higher education, research and innovation, various European research programs, from charity entities - french national programme d'investissement d'avenir: ANR RHU 004; France 2030 IHU-3
  - In 2021/2022 I received honorarium to contribute to advisory board on corticosteroids for sepsis (Pfizer), biomarkers for sepsis (Baxter, Biomerieux), vaccines (Janssen)
- Academic :
  - Contributed to SSC 2008/2012/2016 updates
  - Co-chair the Task Force of CIRCI/corticosteroids in the ICU guidelines, since 2008
  - Corticosteroids for acute inflammation is the main topic of research of my group since 1991
  - Vice president of France Sepsis Association
  - Member of Steering committee of the European Sepsis Alliance
  - Contributor to Sepsis Stronger Together

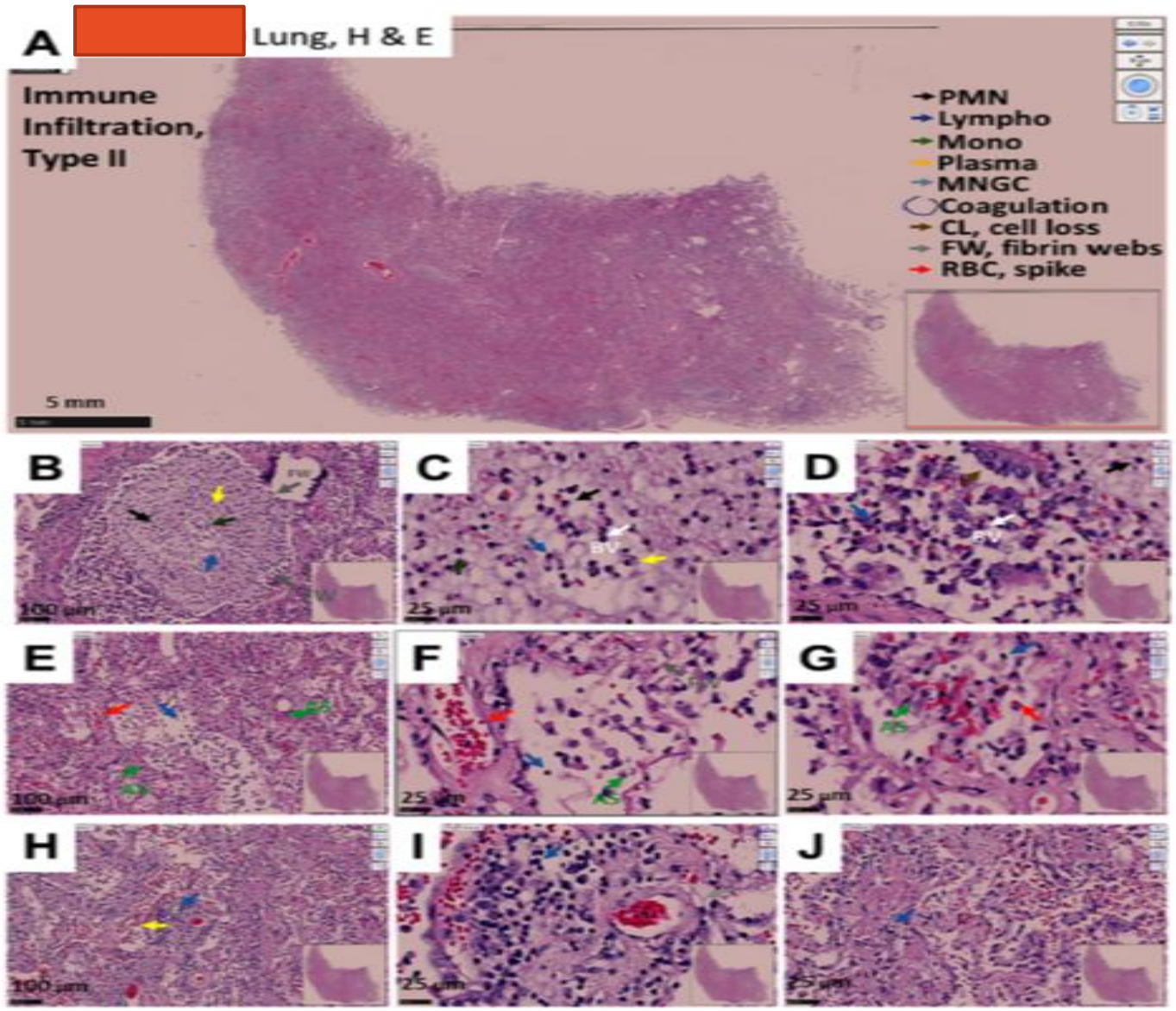
Lower respiratory tract infections place heavy health, social and economic burden



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

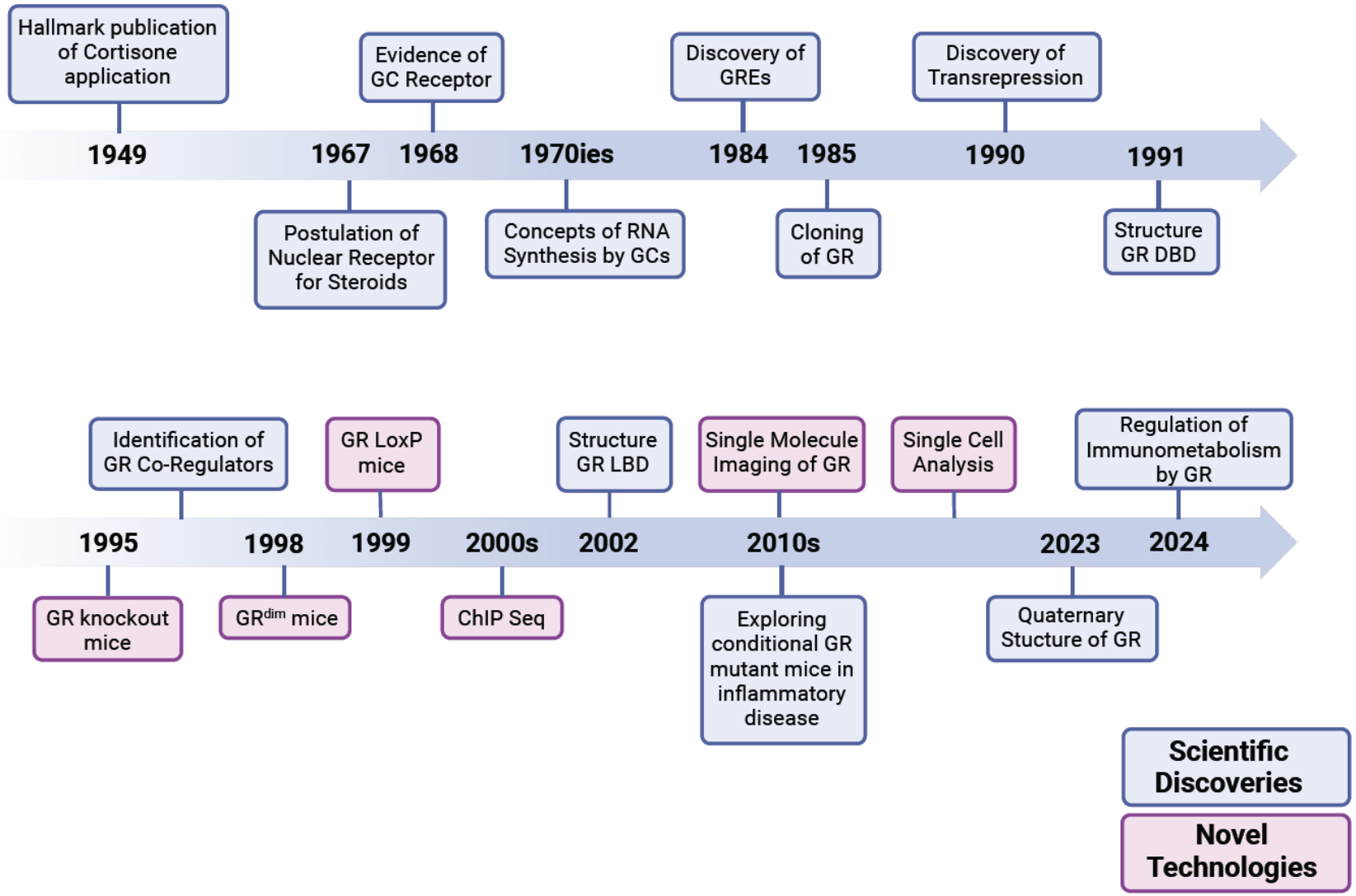
£731 million/year (UK)
16 k€/hosp (France)
55 k$ (USA)

45 years old
Pneumococcal CAP
Died D-7



Pharmacology

The GR Story



Eirs, ann Rheum Dis 2024

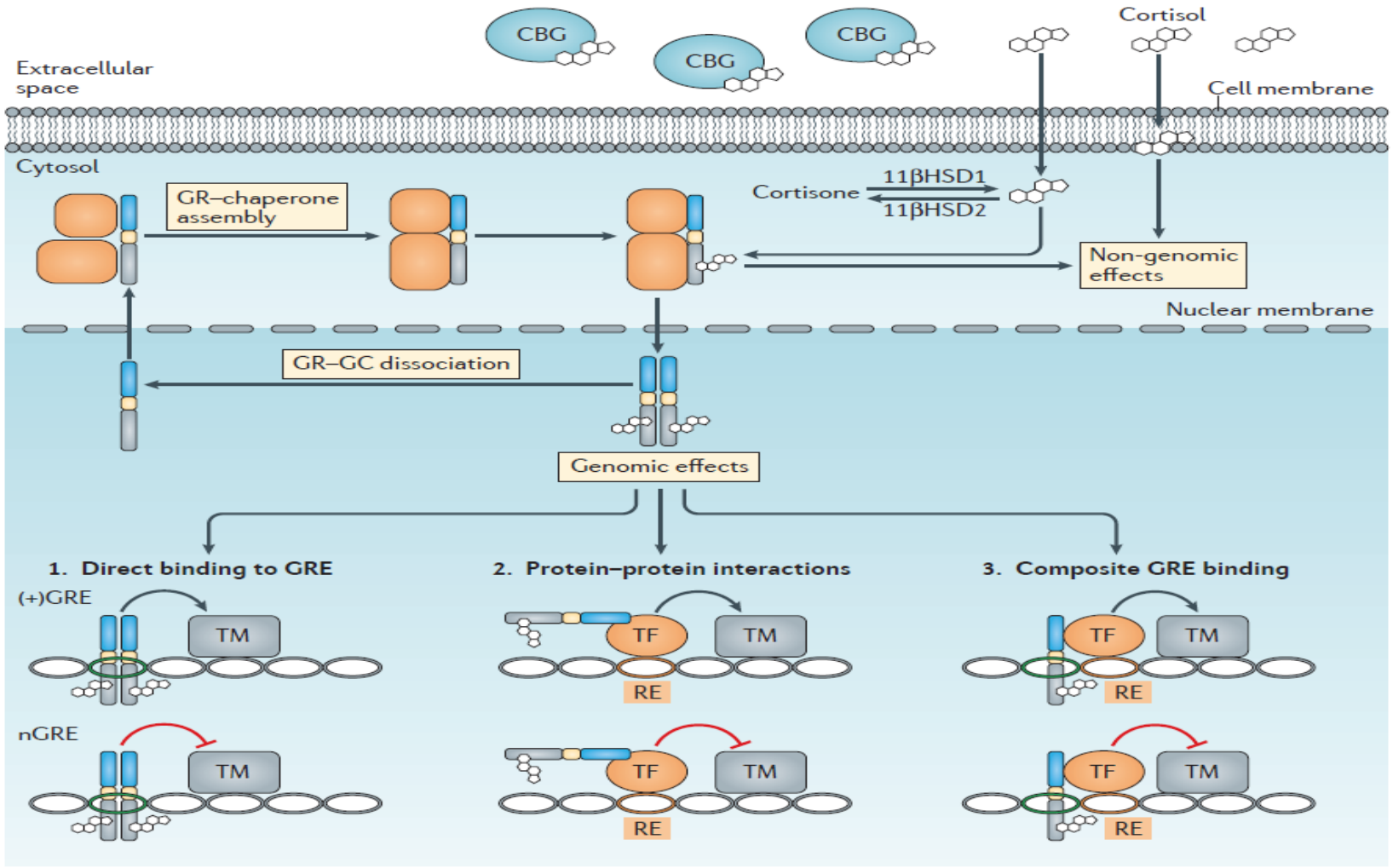
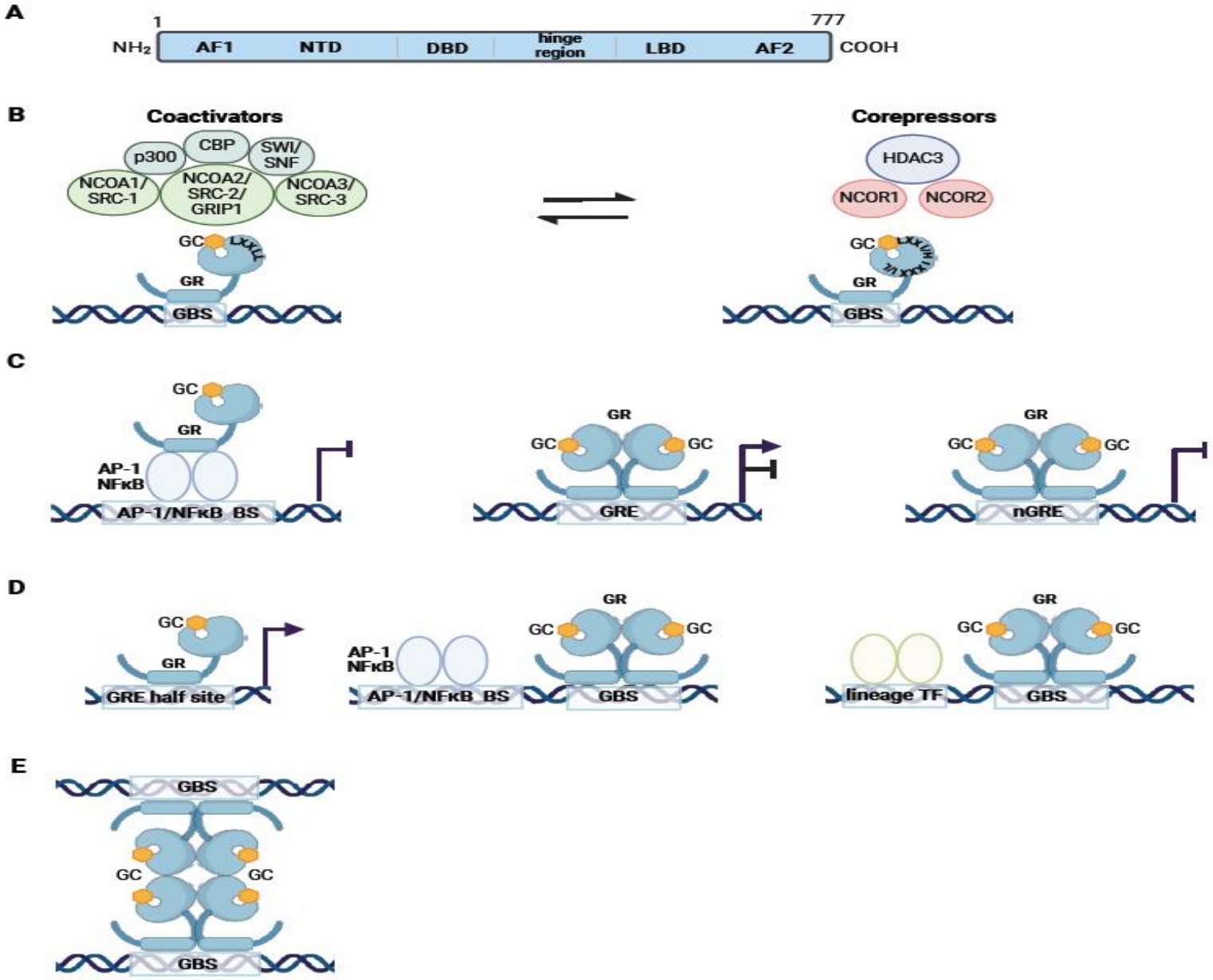


Figure 2 | **Mechanisms of glucocorticoid activity.** In the extracellular space, most endogenous glucocorticoids (GCs)

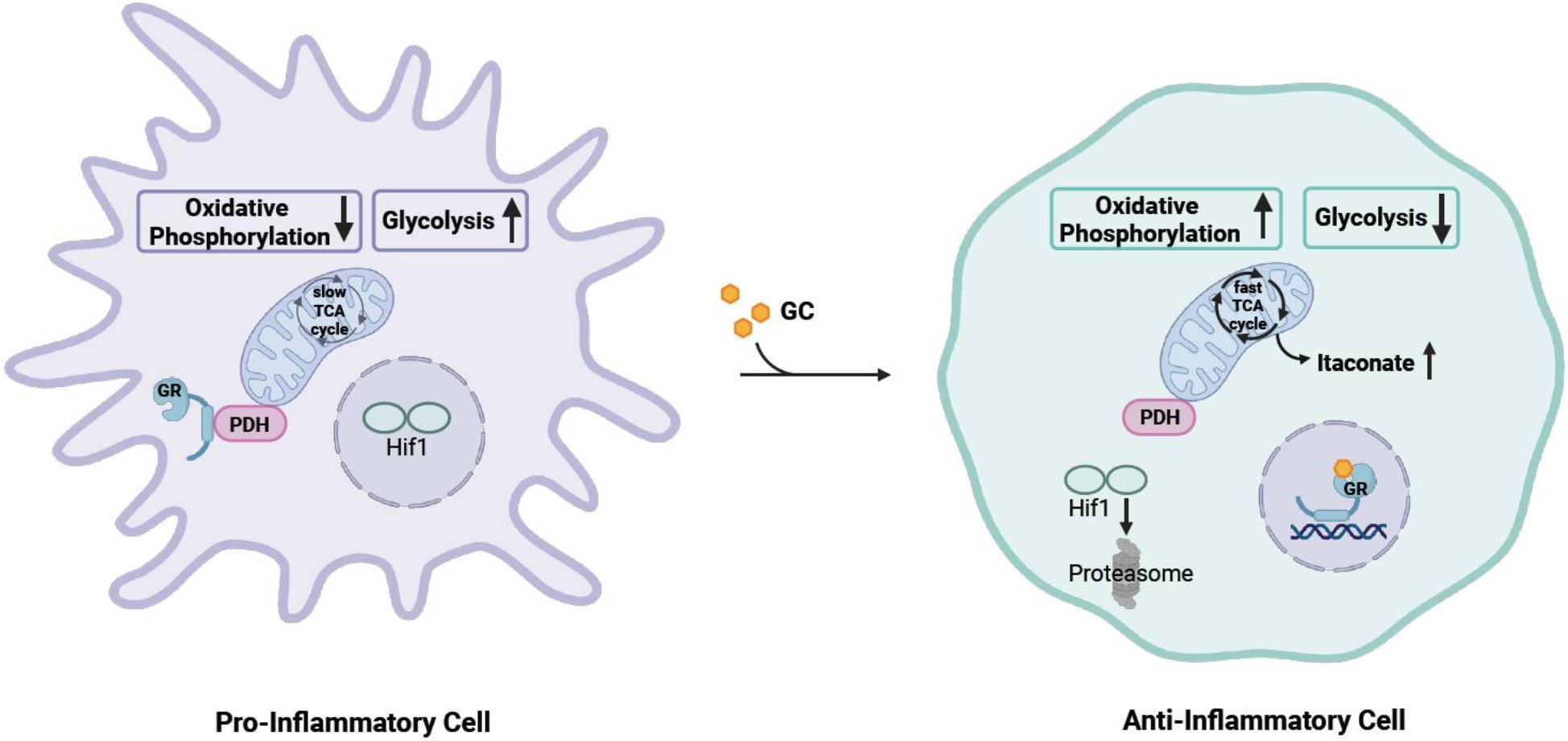
Cain, Nature Rev Immunol 2017

The GR Function

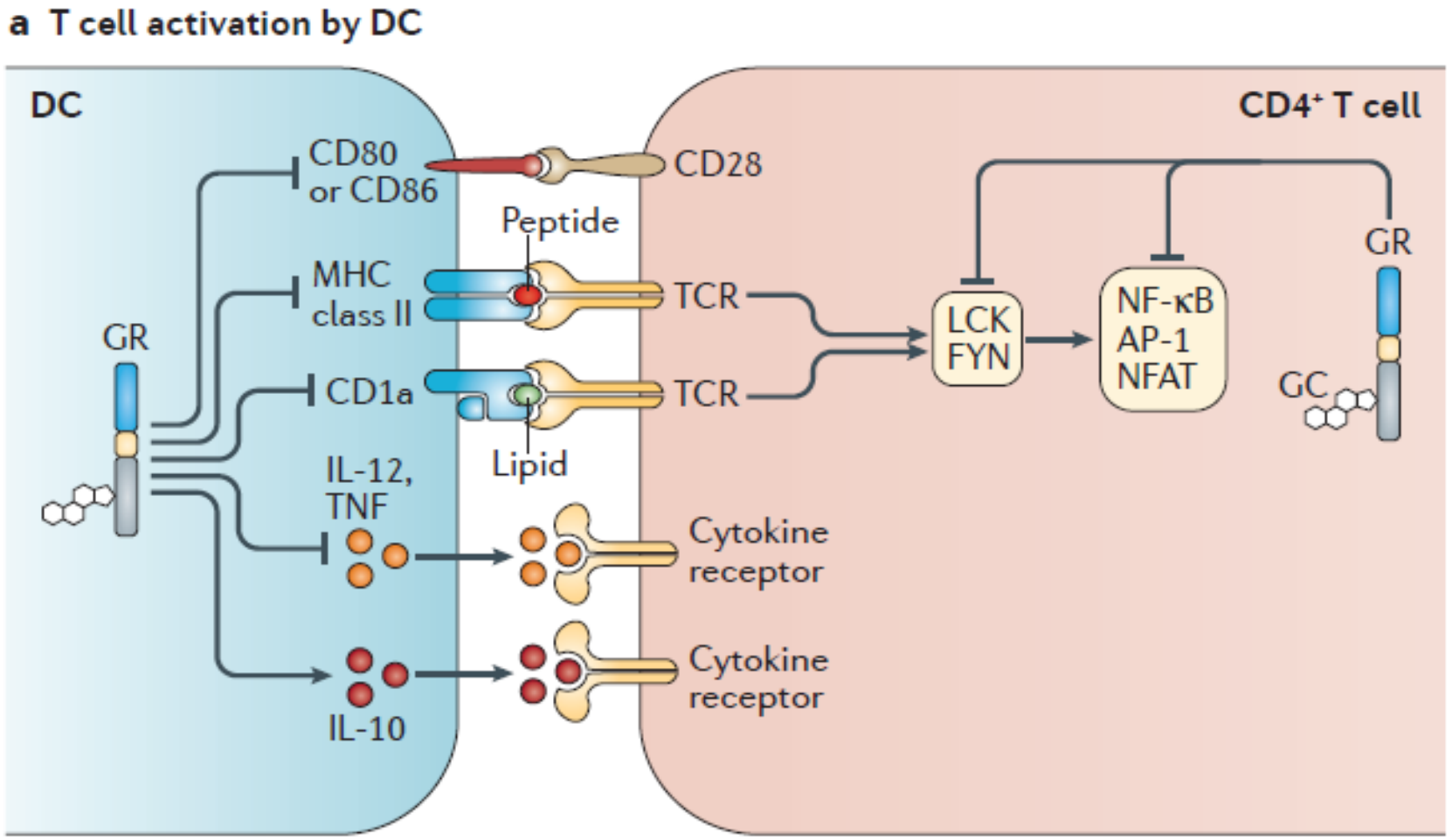


Eirs, Ann Rheum Dis 2024

Effects of Immunometabolism



Eirs, ann Rheum Dis 2024



Cain, Nature Rev Immunol 2017

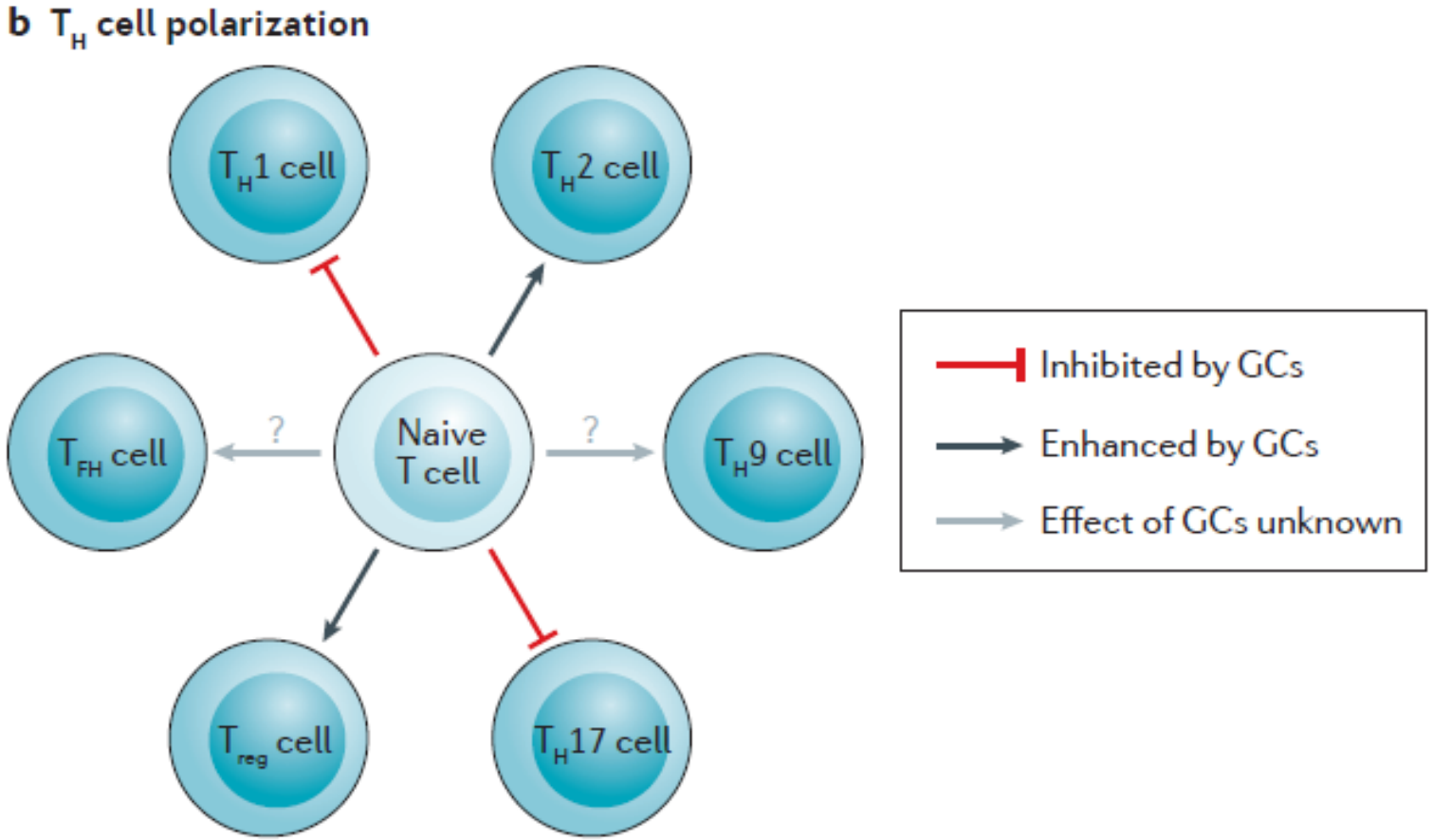
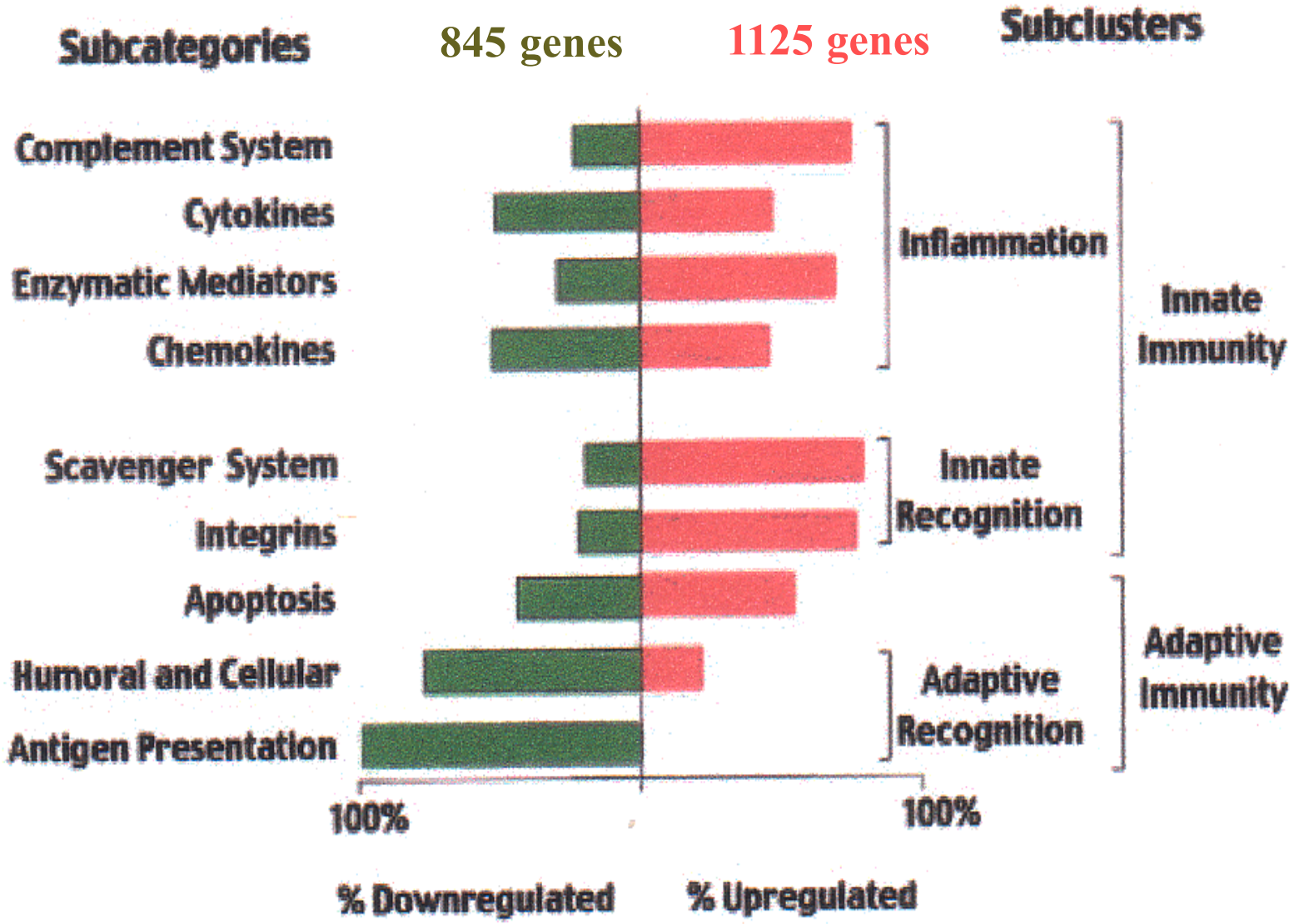


Figure 5 | **Glucocorticoids modulate T cell activity. a** | Glucocorticoids (GCs) suppress

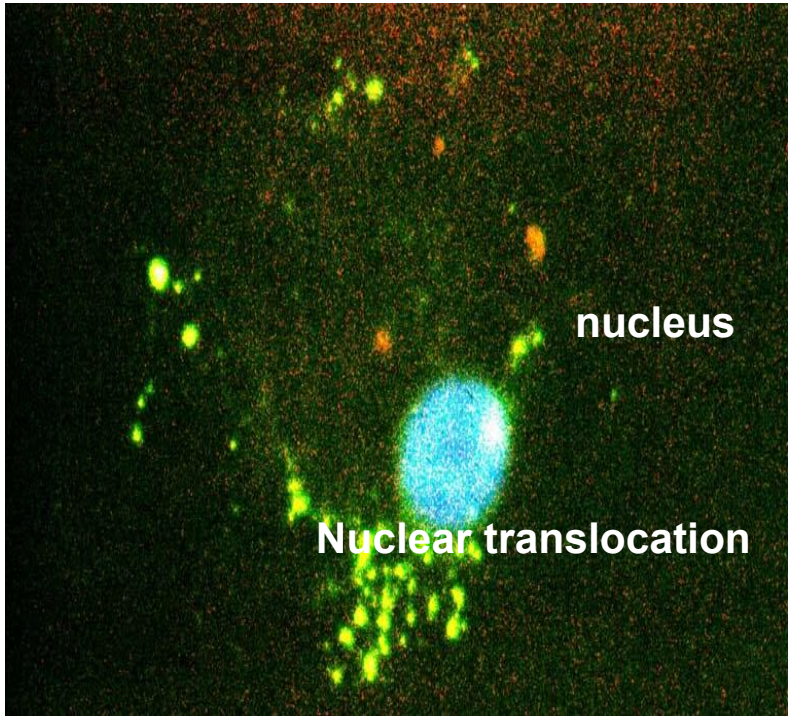
Cain, Nature Rev Immunol 2017

Reprogrammation not suppression!



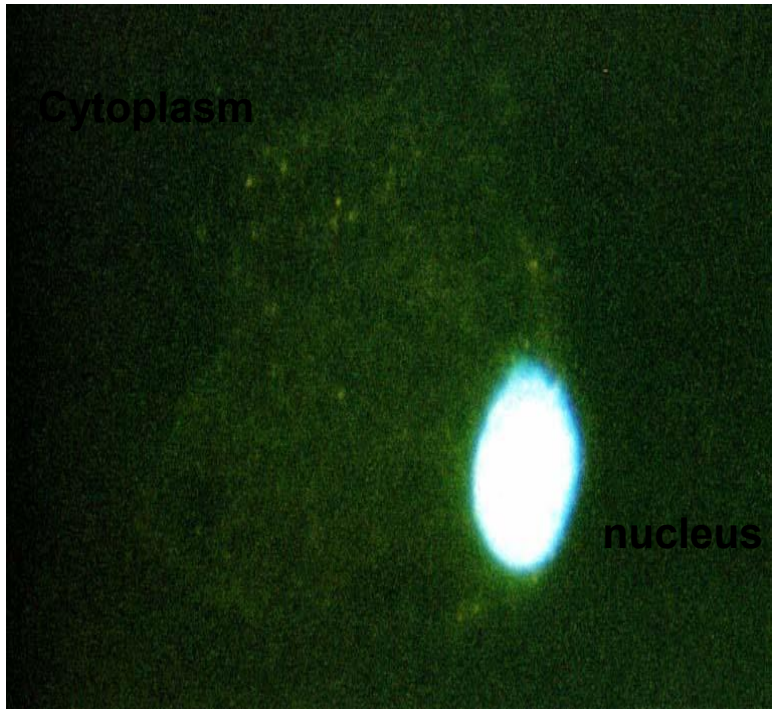
Faseb, 2002

Fluorescent Microscopy
NF-κB localization in the lung



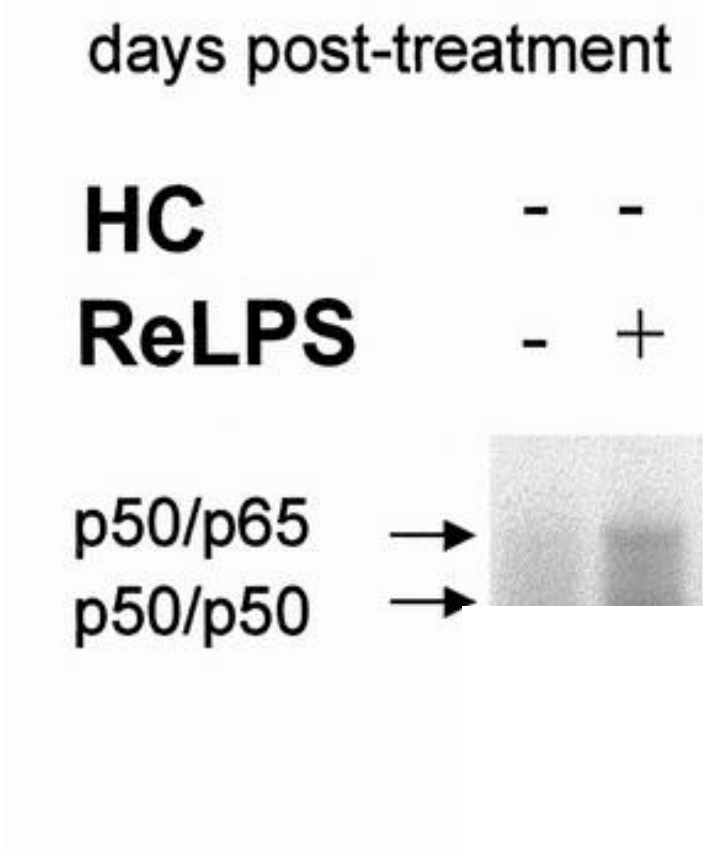
Before steroids

NF-κB staining with FITC-Ab



After 10 days of steroids

Corticosteroids inhibited NF-kB Activation



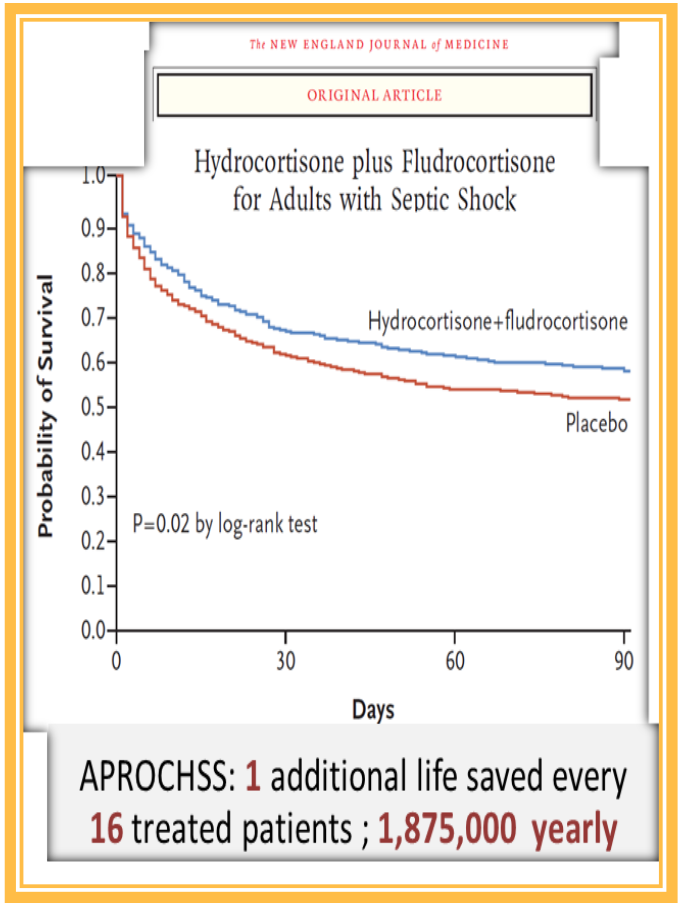
Crit Care Med 2001

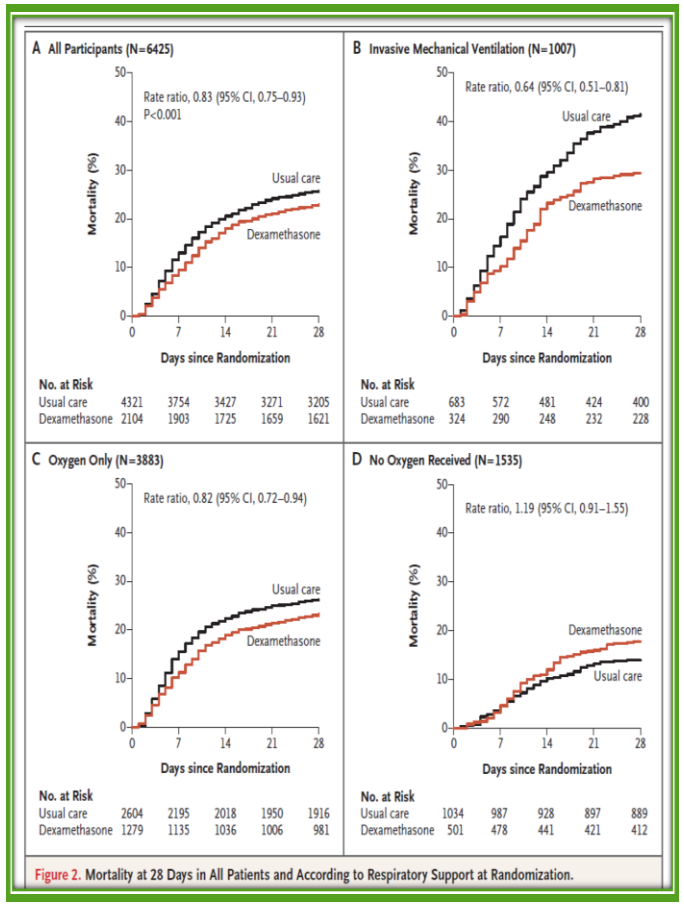
Clinical evidence

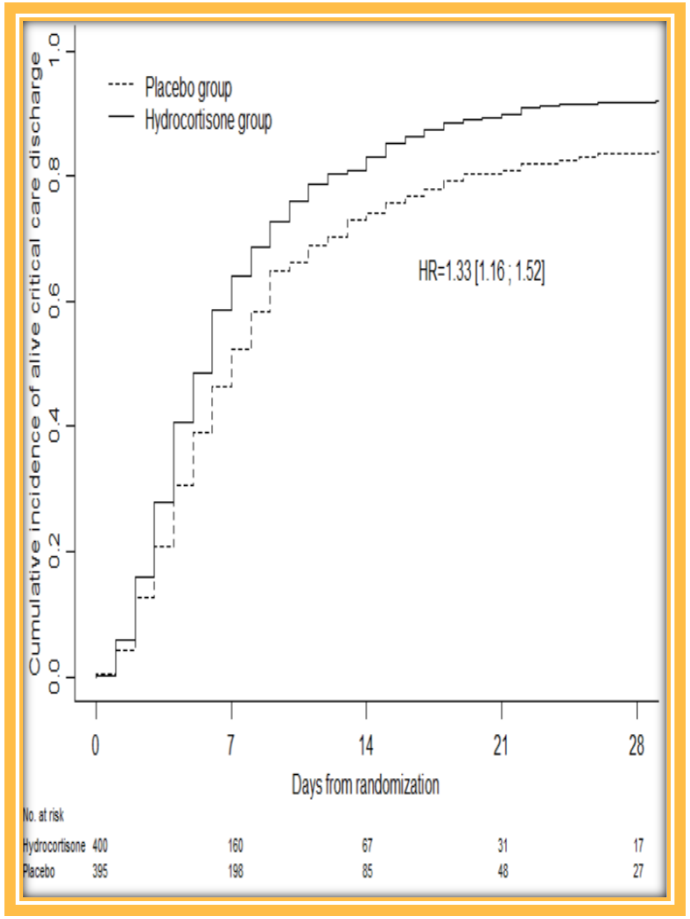
Septic Shock

Severe Covid-19

Severe Community Acquired Pneumonia



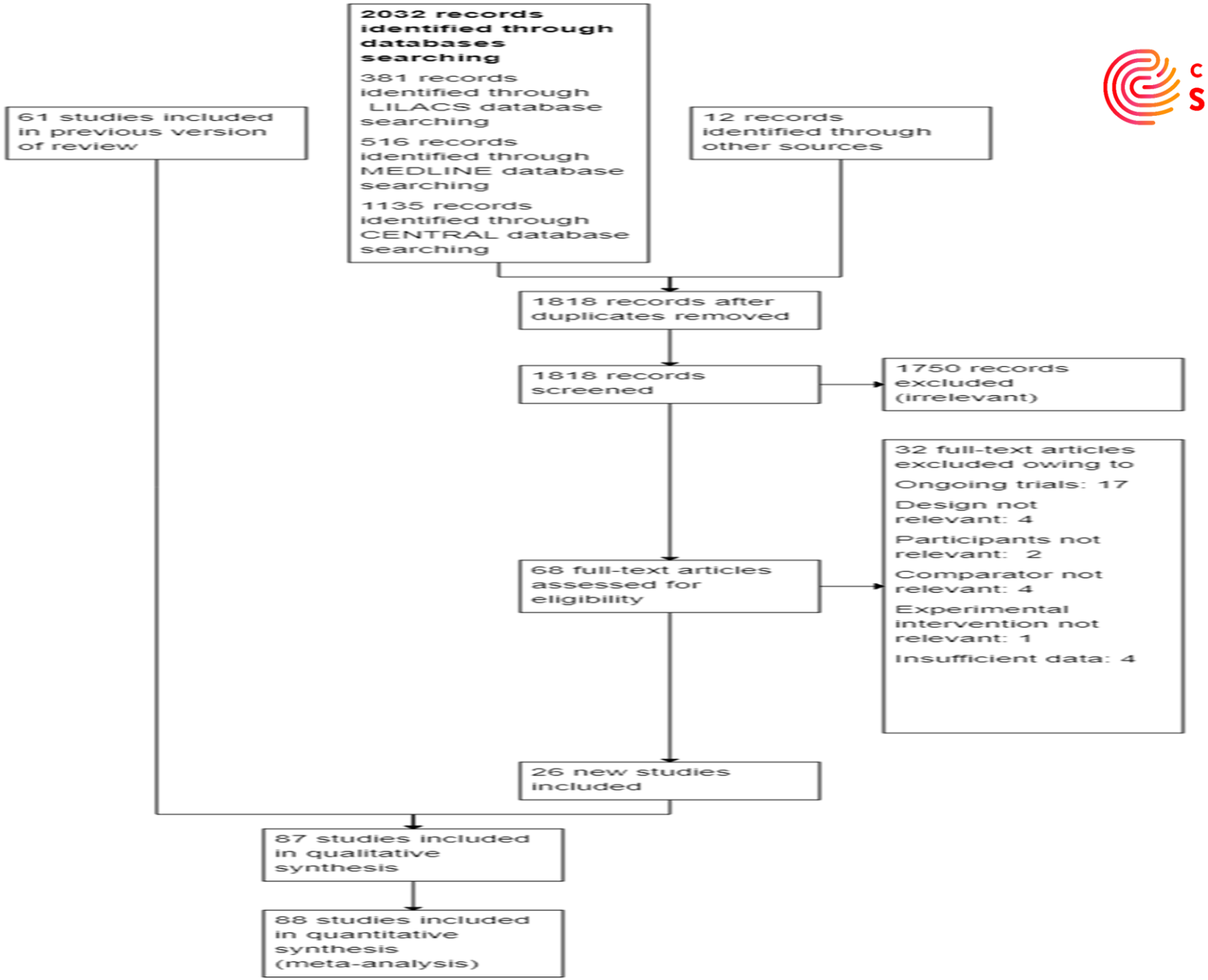




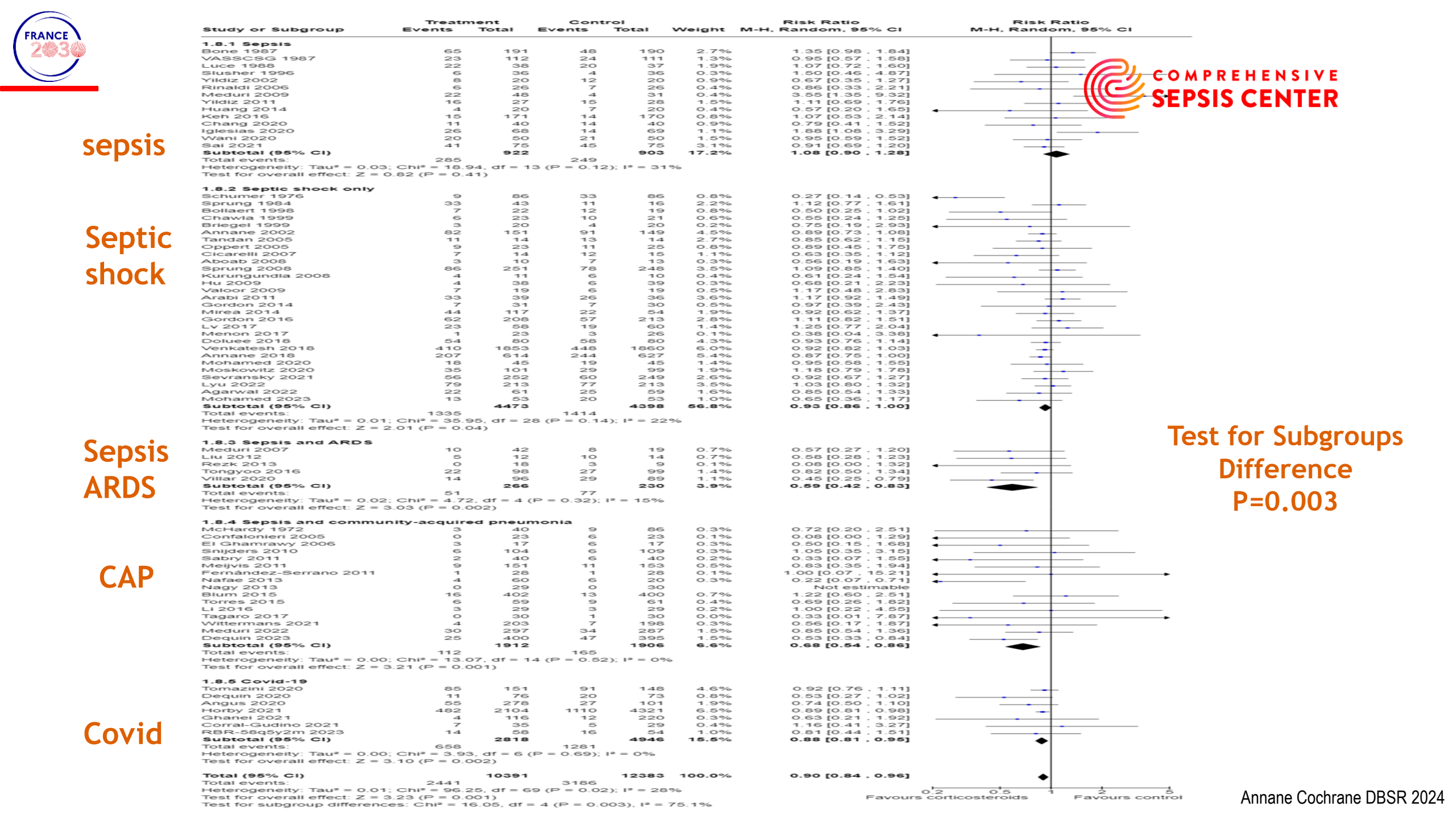
Nejm 2018

Nejm 2021

Nejm 2023



Annane Cochrane DBSR 2025



sepsis

Septic shock

Sepsis ARDS

CAP

Covid

Test for Subgroups Difference P=0.003

Annane Cochrane DBSR 2024

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.

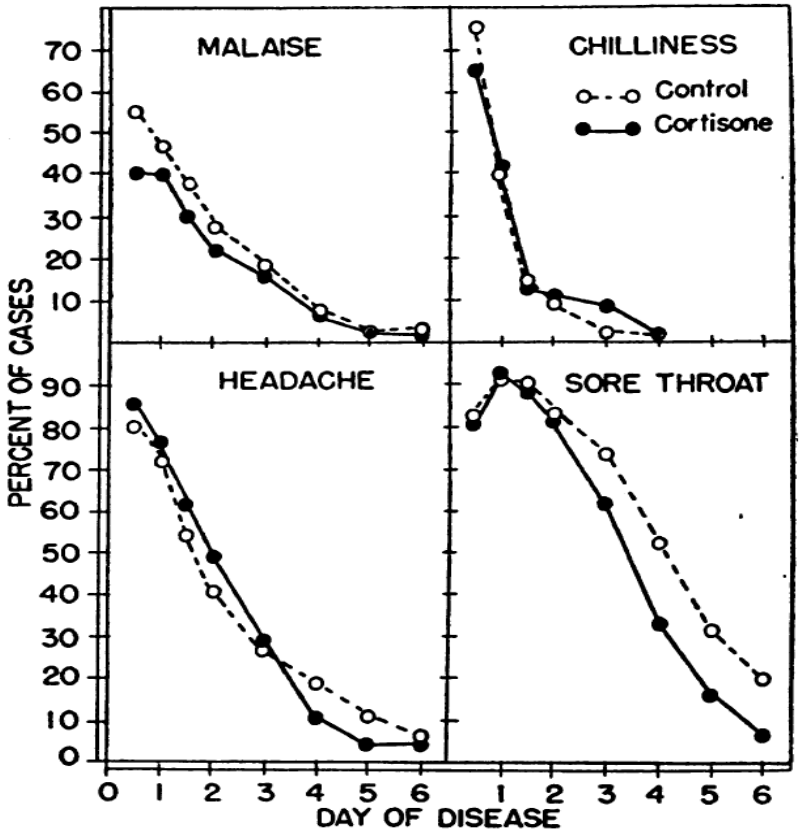


FIG. 1. EFFECT OF CORTISONE THERAPY ON THE SYMPTOMS OF STREPTOCOCCAL TONSILLITIS AND PHARYNGITIS

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

The NEW ENGLAND JOURNAL of MEDICINE

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*

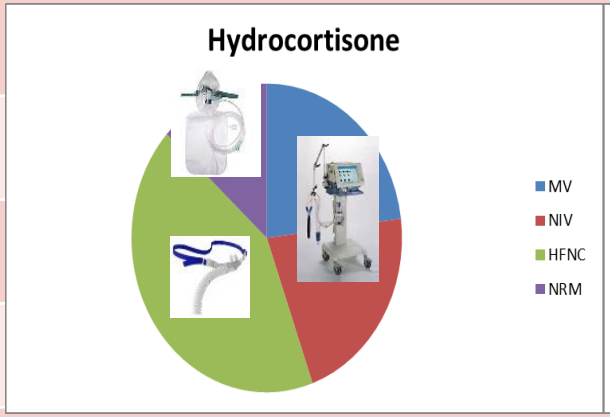
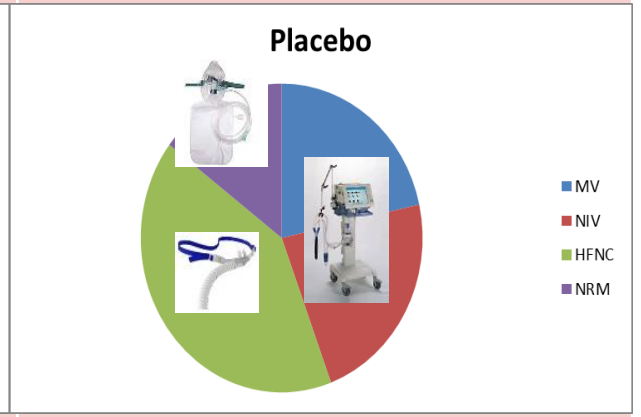
CAPE COD trial

- 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

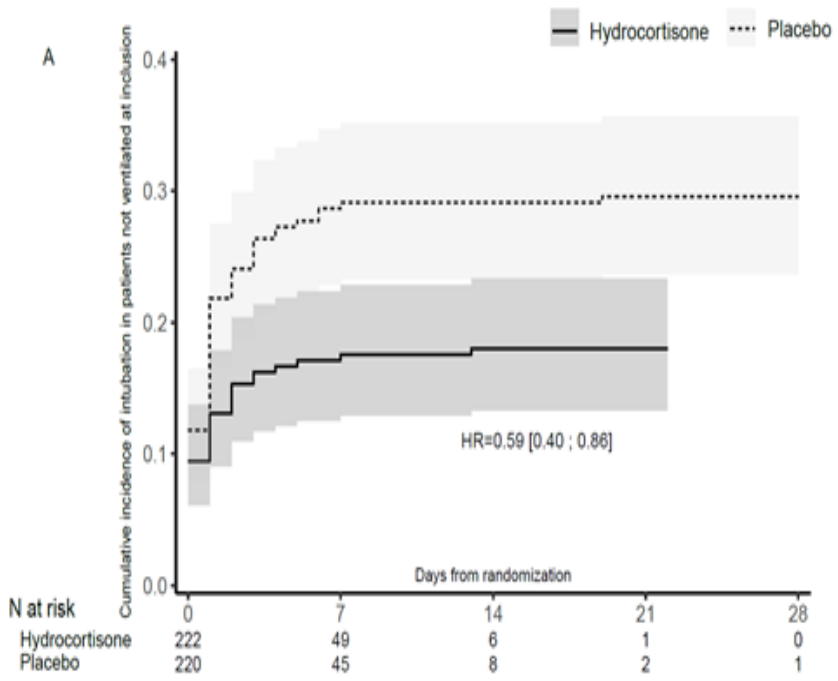
	HC (n=400)	Placebo (n=395)
Age, median (IQR), y	67 (58;77)	67 (58;78)
Male/Female, %	70.3/29.7	68.3/31.4
Respiratory support		
PaO_2/FiO_2, median (IQR)	143 (104;195)	137 (96;192)
SAPS II, median (IQR)	37 (30;45)	38 (31;47)
SOFA, median (IQR)	4 (3;6)	4 (3;6)

Results: mortality

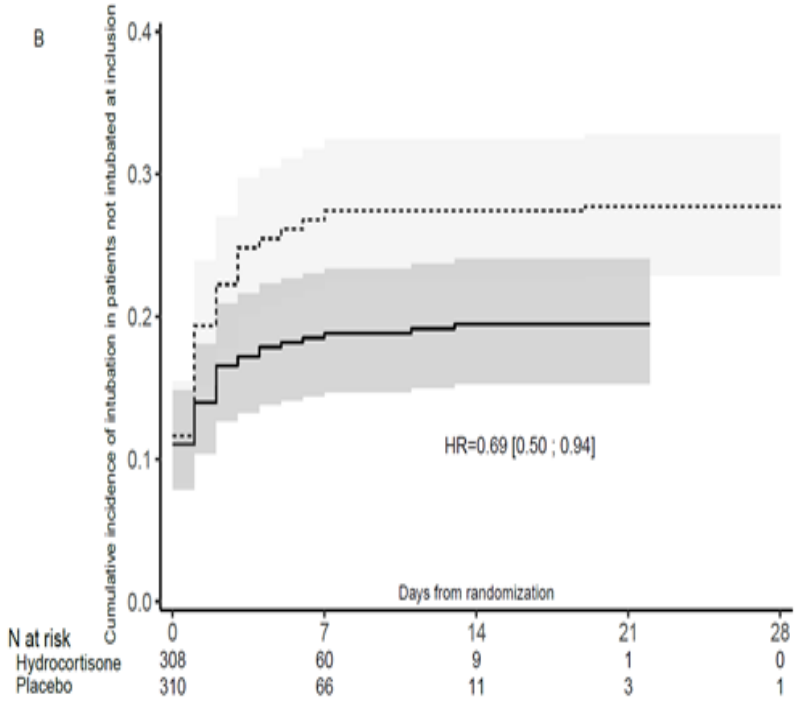
	HC (n=400)	Placebo (n=395)	Difference	P
Death D28	6.3% [3.9;8.6]	11.9% [8.7;15.1]	-5.6 [-9.6;-1.7]	0.0055
Death D90	9.3% [6.4;12.2]	14.7% [11.1;18.2]	-5.4 [-9.9;-0.8]	0.02

Cumulative incidence of intubation

Among 442 non NM patients

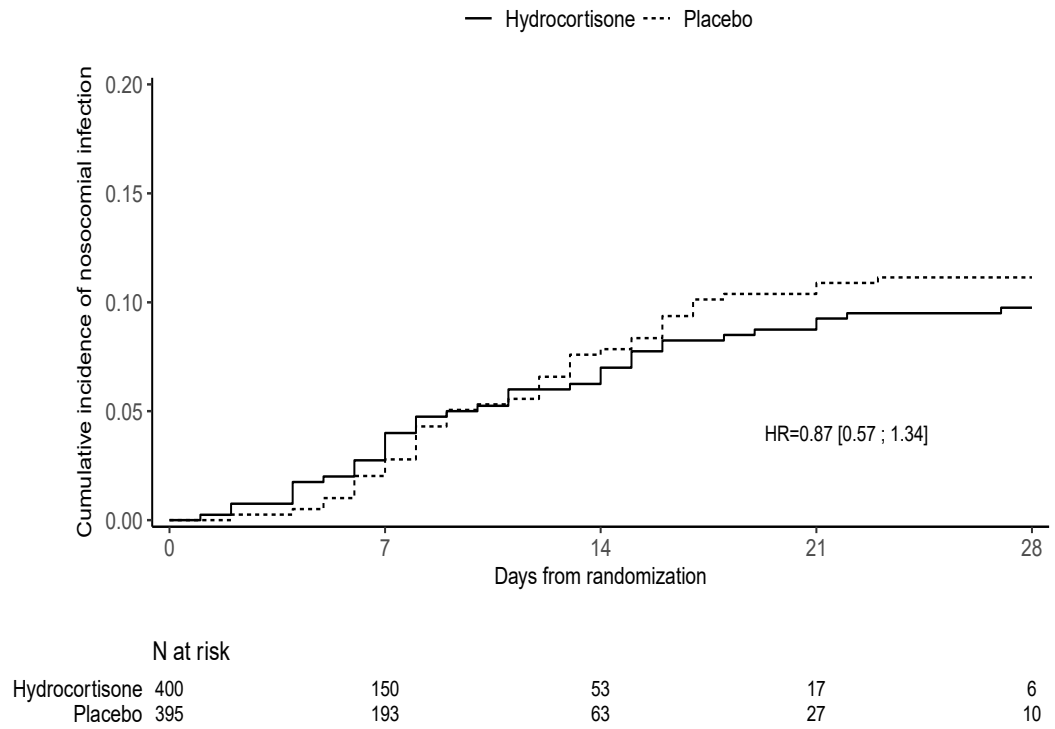


Among 618 non IMV patients



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

Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial

Nicholas Heming, Alain Renault, Emmanuelle Kuperminc, Christian Brun-Buisson, Bruno Megarbane, Jean-Pierre Quenot, Shidasp Siami,

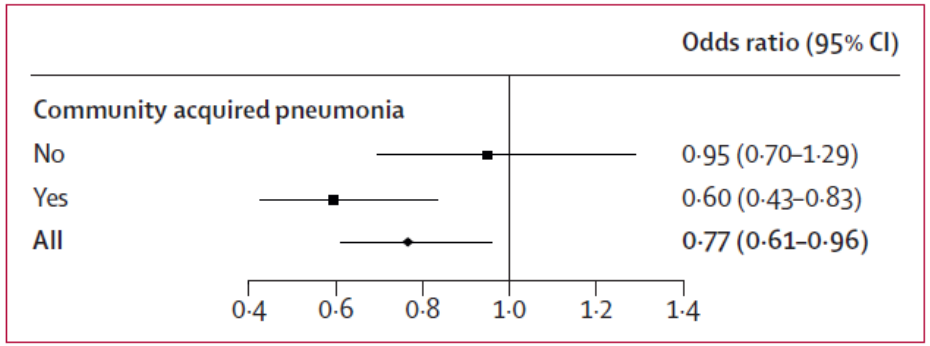
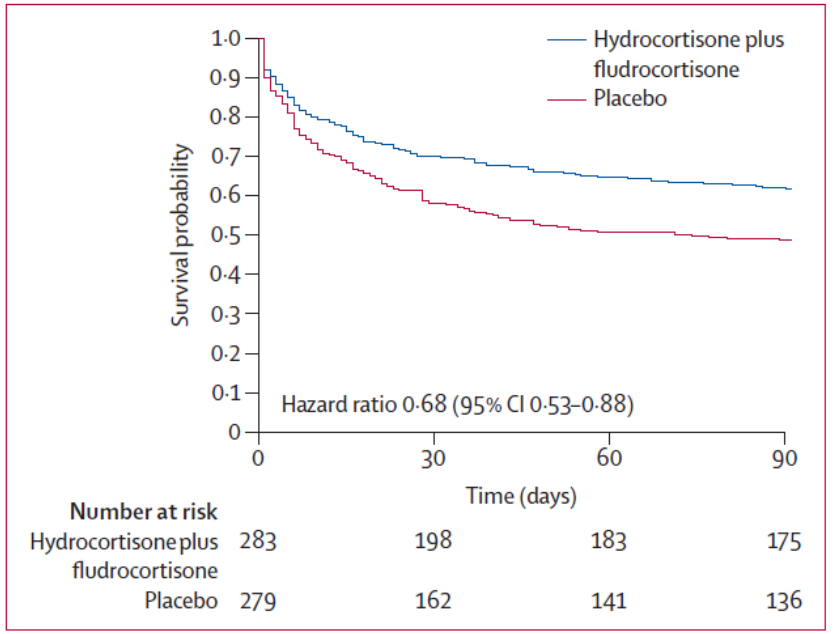
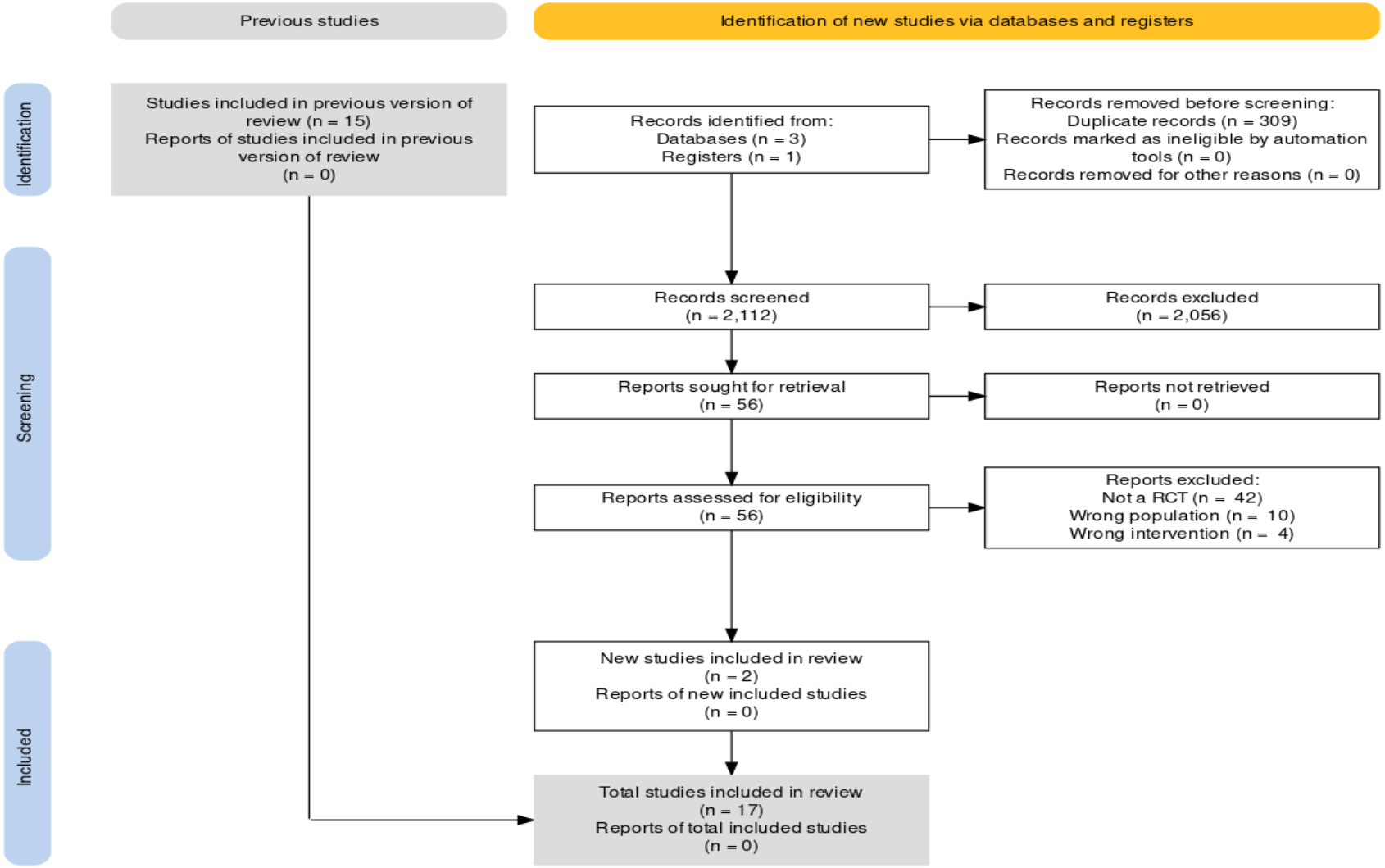


Figure 1: **Forest plot of corticosteroid effects across subgroups with or without community acquired pneumonia**
Odds ratio and 95% CI for 90-day all-cause mortality in the whole population and in the subgroups with or without community acquired pneumonia. There was a significant statistical heterogeneity in corticosteroid effects on 90-day mortality across subgroups with or without community acquired pneumonia (multiplicative interaction p=0·046 and additive interaction p=0·046).

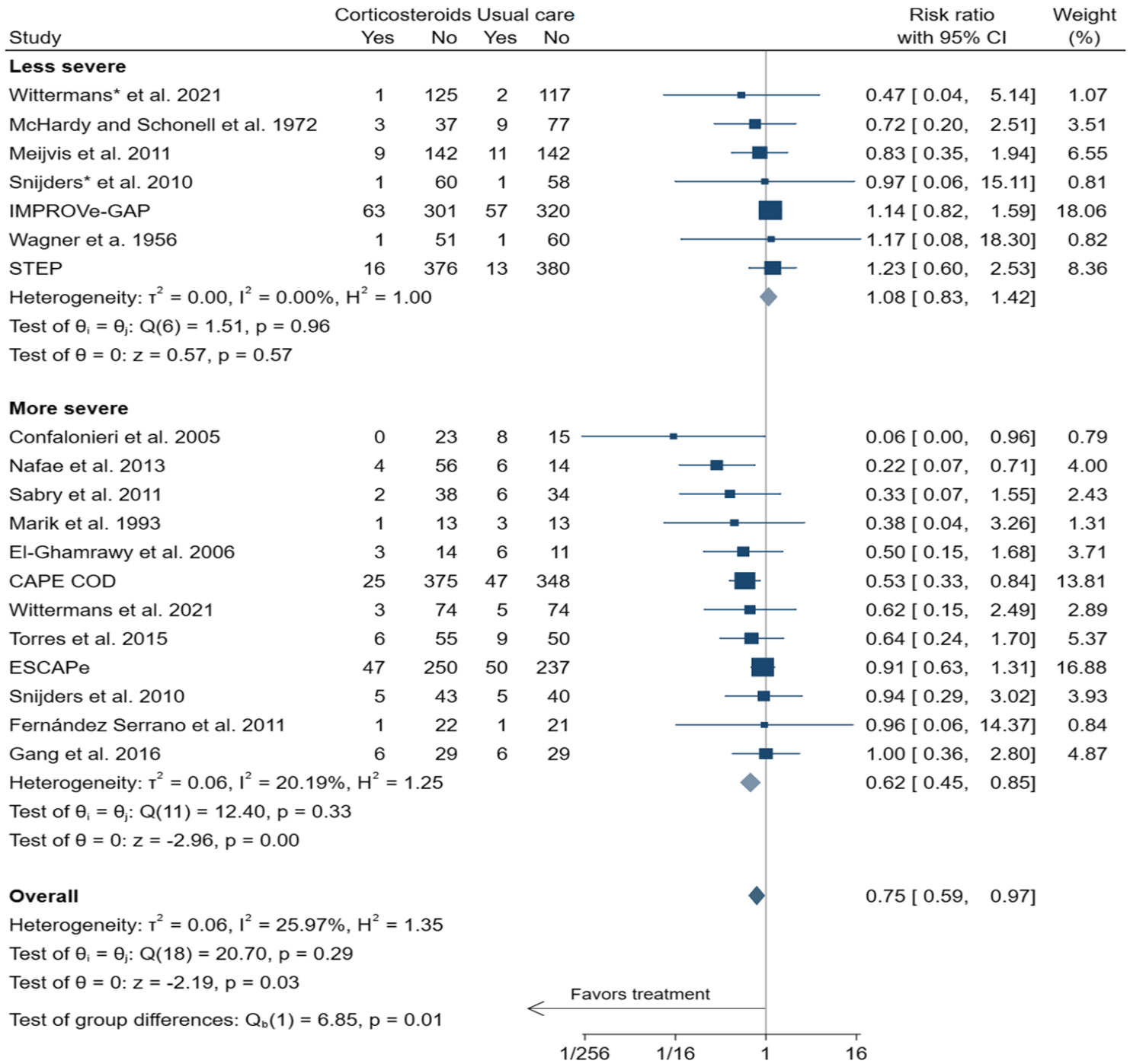


Corticosteroids in CAP : A SR, pairwise and dose response meta-analysis



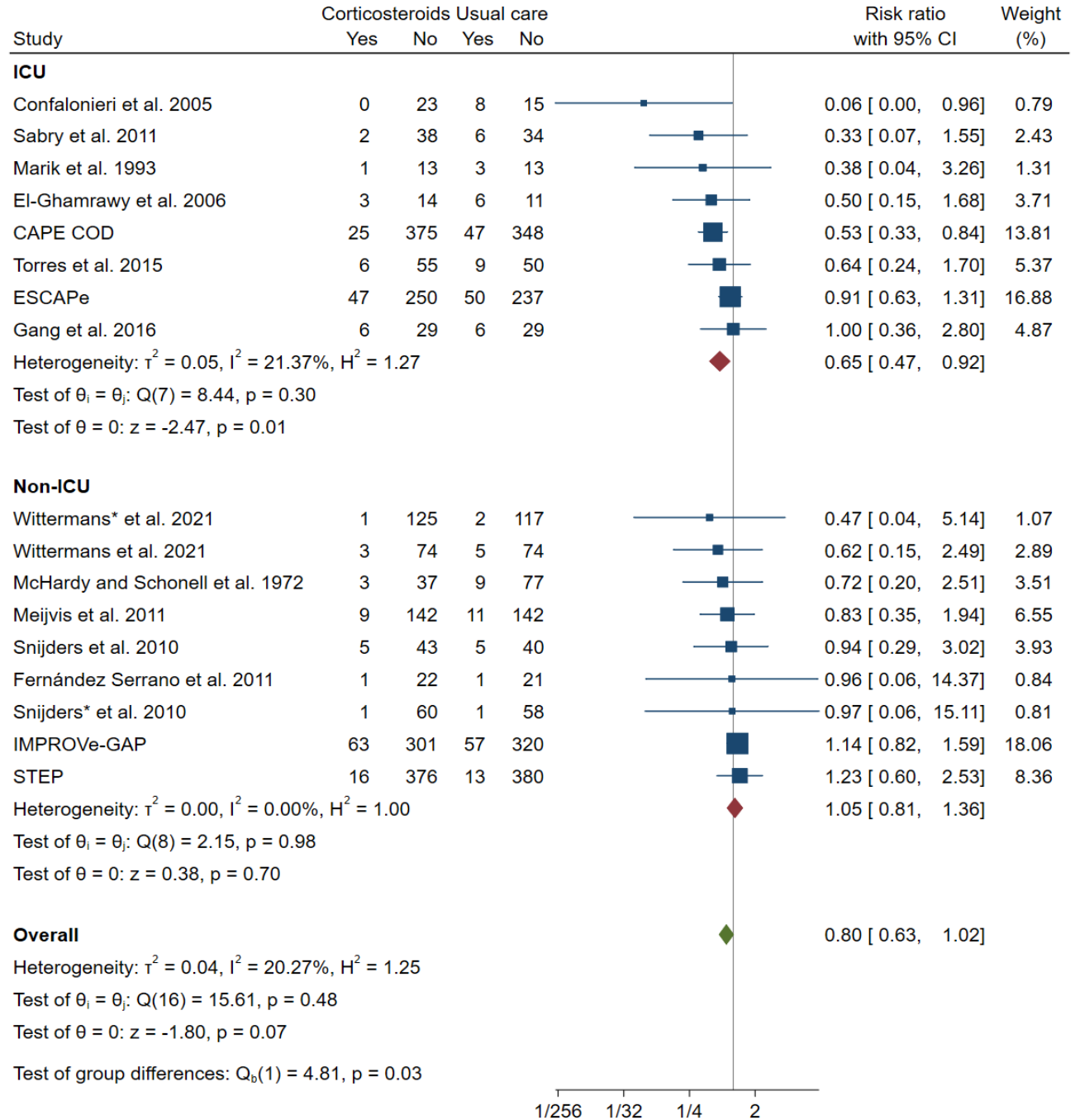
Pitre ICM 2025

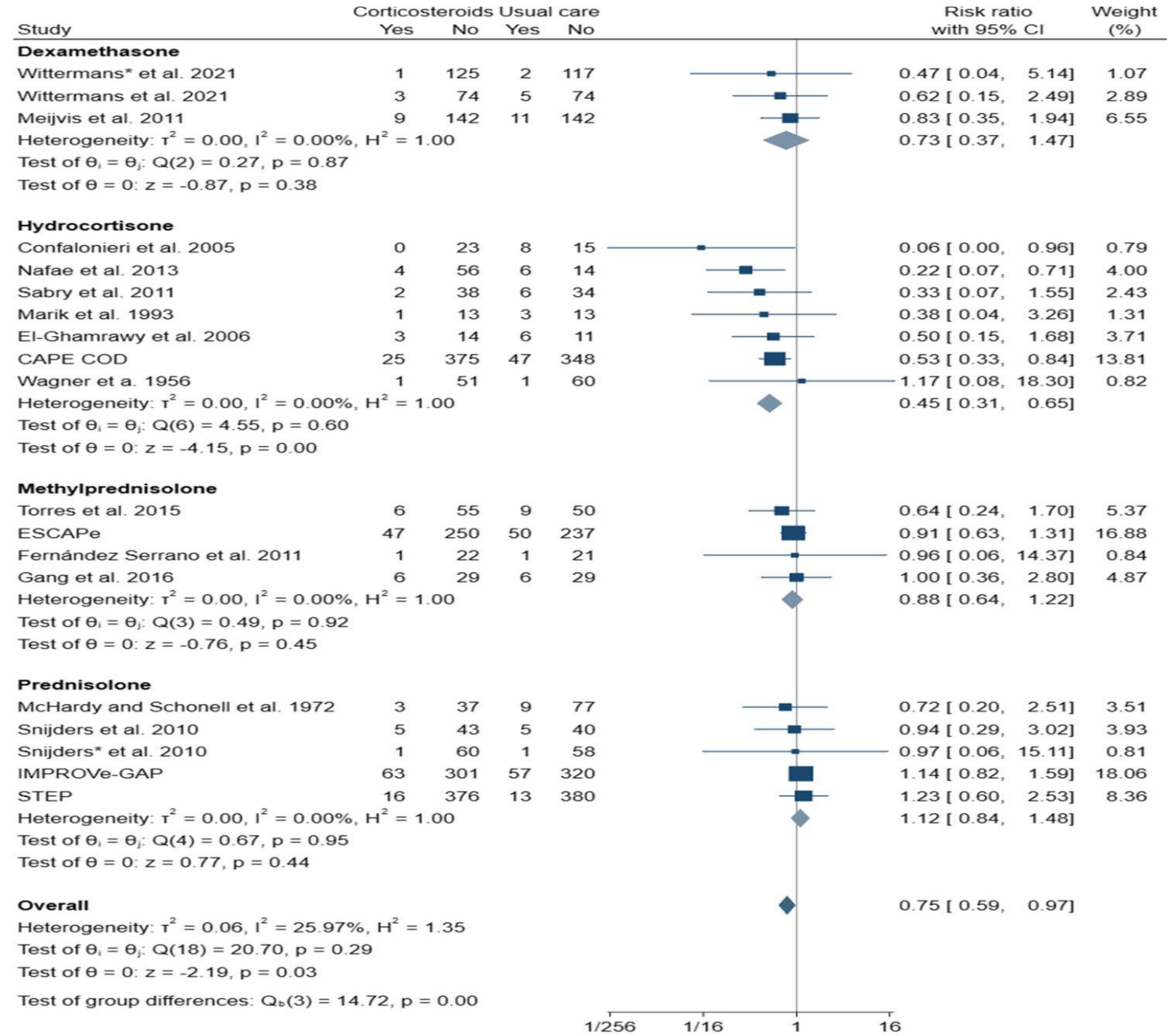
Mortality



Pitre ICM 2025

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: τ² = 0.05, I² = 21.37%, H² = 1.27 0.65 [0.47, 0.92]
Test of θi = θj: Q(7) = 8.44, p = 0.30
Test of θ = 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: τ² = 0.00, I² = 0.00%, H² = 1.00 1.05 [0.81, 1.36]
Test of θi = θj: Q(8) = 2.15, p = 0.98
Test of θ = 0: z = 0.38, p = 0.70
Overall 0.80 [0.63, 1.02]
Heterogeneity: τ² = 0.04, I² = 20.27%, H² = 1.25
Test of θi = θj: Q(16) = 15.61, p = 0.48
Test of θ = 0: z = -1.80, p = 0.07
Test of group differences: Qb(1) = 4.81, p = 0.03
1/256
1/32
1/4
2
Random-effects REML model



Pitre ICM 2025

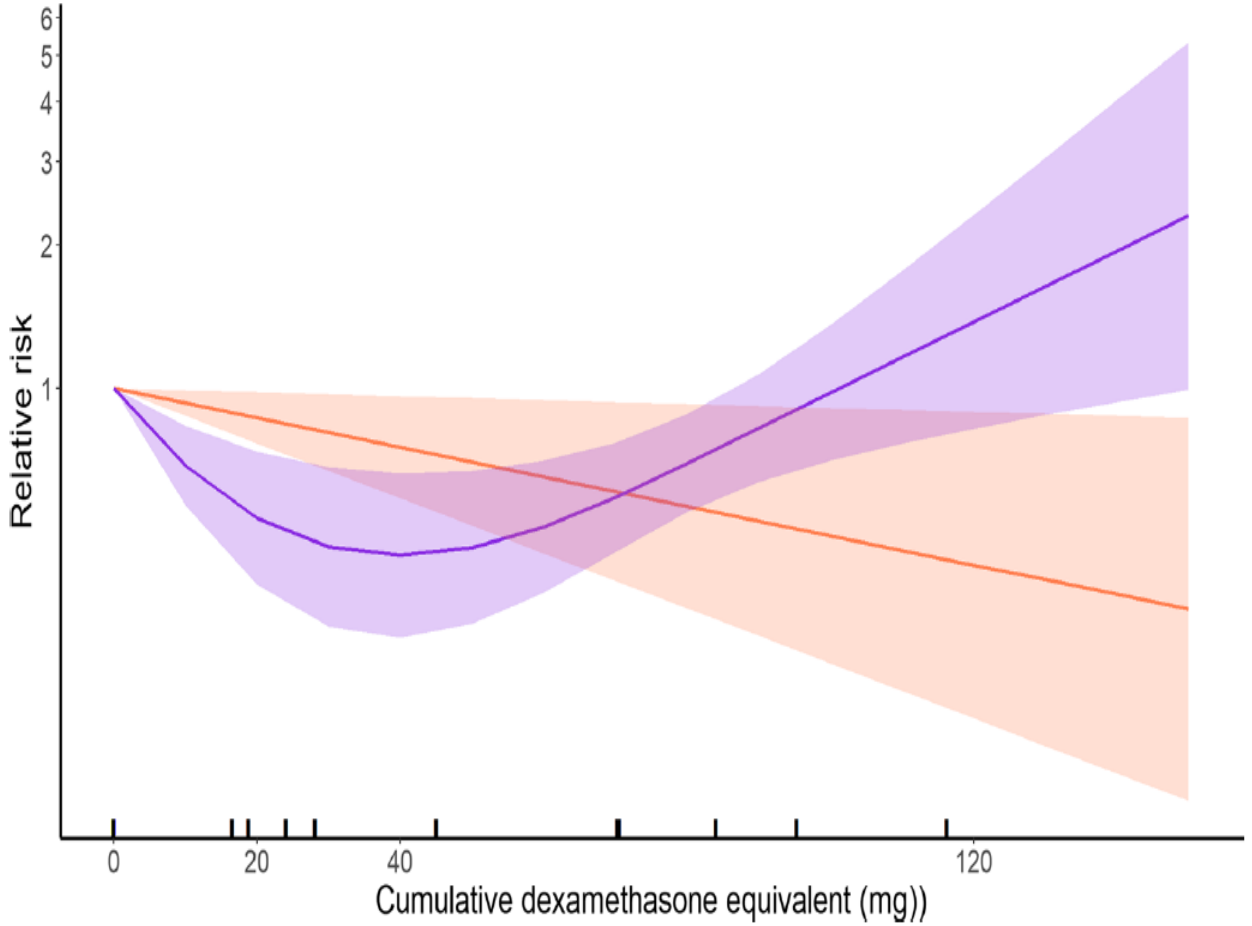
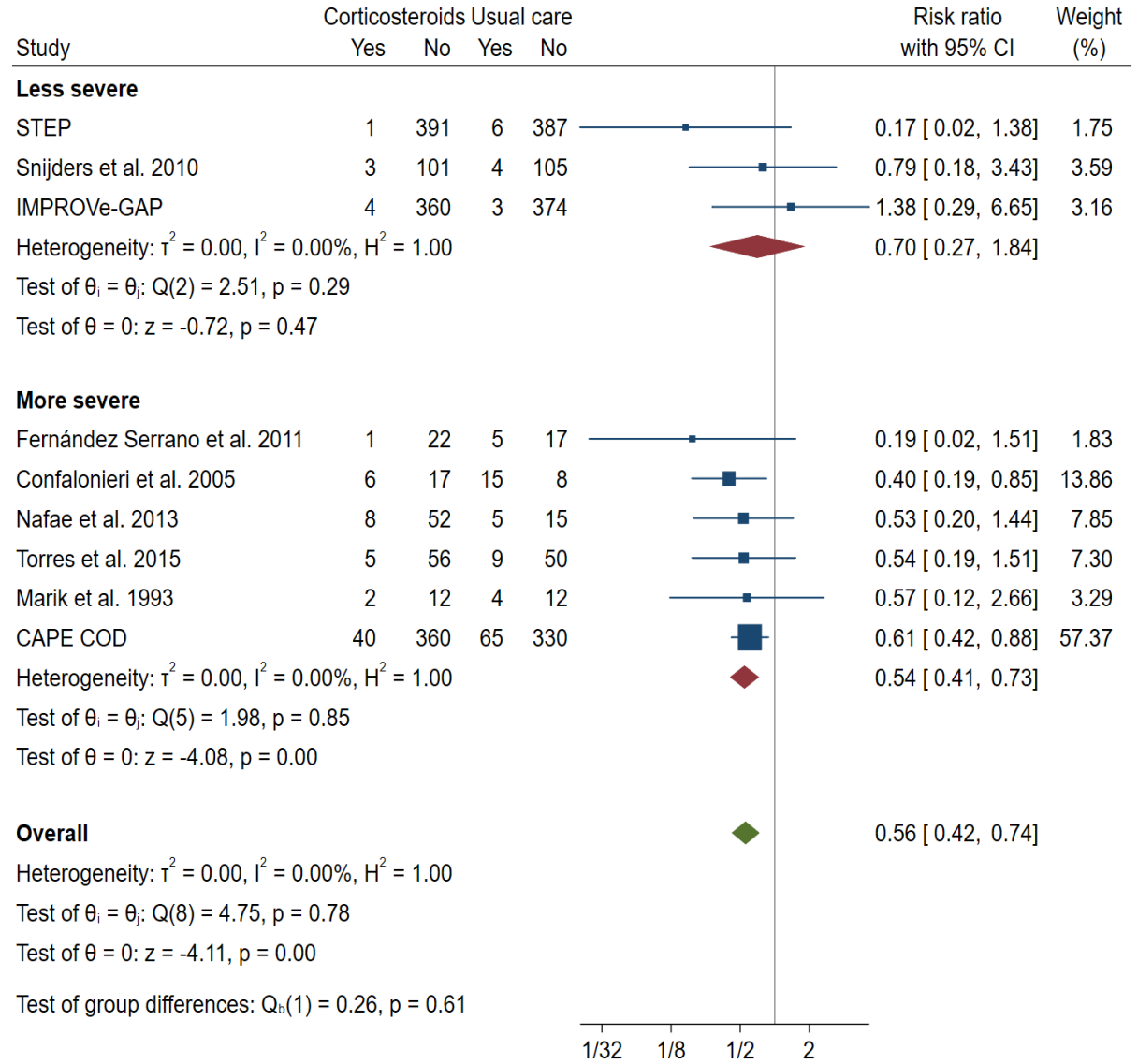
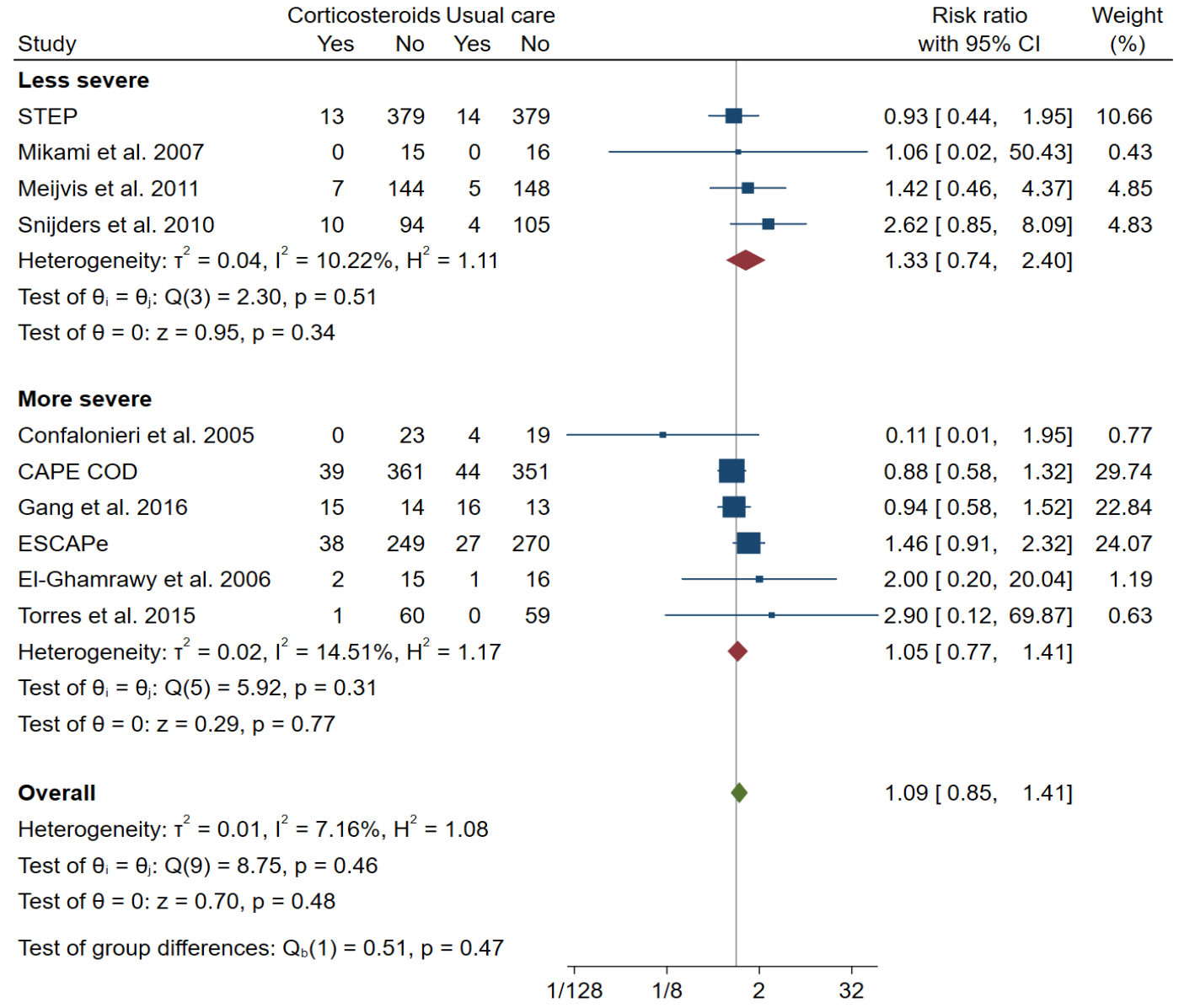


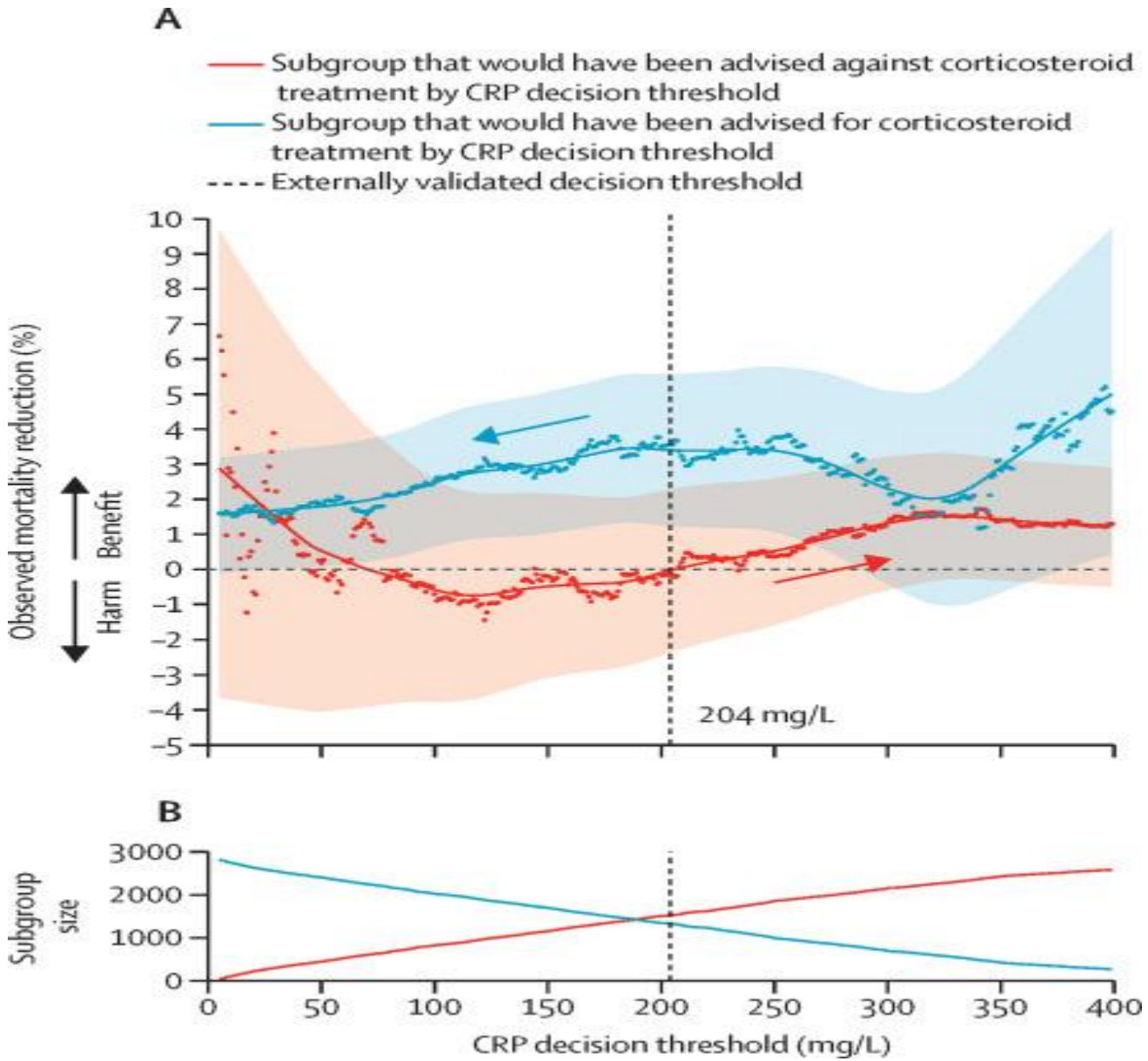
Figure 4 Dose-response curve. The curved purple line represents the non-linear dose-response relationship, and the purple ribbons represent 95% confidence intervals (95% CI). The yellow linear line represents the linear dose-response relationship, and the ribbons represent 95% CI.

Need for IMV


Corticosteroids Usual care
Study Yes No Yes 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: τ² = 0.00, I² = 0.00%, H² = 1.00 0.70 [0.27, 1.84]
Test of θi = θj: Q(2) = 2.51, p = 0.29
Test of θ = 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: τ² = 0.00, I² = 0.00%, H² = 1.00 0.54 [0.41, 0.73]
Test of θi = θj: Q(5) = 1.98, p = 0.85
Test of θ = 0: z = -4.08, p = 0.00
Overall 0.56 [0.42, 0.74]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(8) = 4.75, p = 0.78
Test of θ = 0: z = -4.11, p = 0.00
Test of group differences: Qb(1) = 0.26, p = 0.61
1/32 1/8 1/2 2
Random-effects REML model

Risk for secondary Infections





Smit LRM 2025

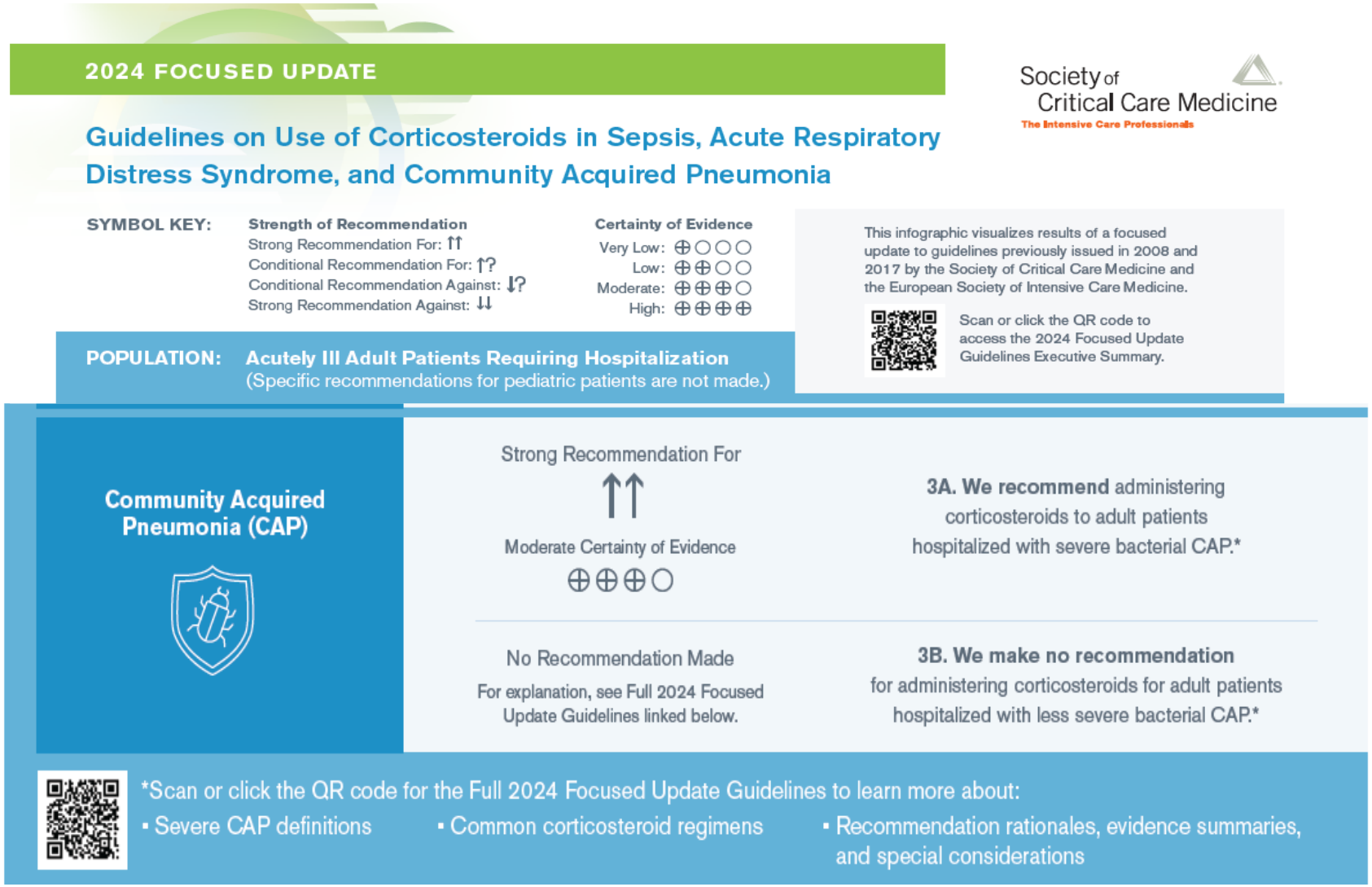
French Guidelines

The 2025 guidelines

- In non-severe (outpatient or hospitalized) CAP, the addition of corticosteroids is not recommended (**Grade A-2**).
- In severe (hospitalized in critical care) CAP, the addition of hydrocortisone hemisuccinate started during the first 24 h following the onset of severity signs is recommended, except in cases of myelosuppression, aspiration pneumonia, or influenza etiology. The initial dose is 200 mg per day, with reevaluation on the 4th day to determine dose tapering and a total duration ranging from 8 to 14 days (**Grade A-1**).

Dinh Res Med Res, 2025

SCCM Guidelines



Chaudury CCM, 2024

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